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THE
CLINICAL PATHOLOGY
OF
THE BLOOD.

BY

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TRANSLATED FROM THE SECOND GERMAN EDITION

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TRANSLATORS' PREFACE.

THE following translation was authorised by Professor v. Limbeck shortly before his premature death, and represents the latest German edition save for the fact that Dr. Freund's chapter, which deals chiefly with the physiological aspects of blood coagulation, and certain other passages have been considerably condensed.

Professor v. Limbeck had a world-wide reputation as an authority upon all points connected with the physiology, pathology, and chemistry of the blood, and his early death was a heavy blow to every one interested in these subjects. He was a man of singularly engaging nature and of enormous capacity for work, and notwithstanding the many calls upon his time, was ever ready to help any who, like ourselves, had the inestimable privilege of working with him. In addition to this Professor v. Limbeck combined many qualities which are not always associated with great learning. He was generously appreciative of the work done by others; whilst on those rare occasions on which he was shown to be at fault, he was the first to admit his error. A touch of quiet humour and gentle satire also characterised him, as may be seen in the few but telling words with which he dismisses the plausible theory of Bunge, and the preposterous one of Neusser.

Ehrlich's work on the differential staining properties of

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blood-corpuscles gave a great impetus to the microscopical study of hæmatology, and hundreds of observers devoted themselves, for a time, to this branch of science. Professor v. Limbeck endeavoured to collect and edit all the more important facts that were thus scattered over scientific literature. The value of the material which he brought together in the following pages is enhanced by illustrations from his clinical and experimental observations, and by many suggestive theories and criticisms of his own. The work gives a clear and sound idea of the present state of hæmatology, and should be of great service to those working at this subject, in view of the enormous amount of information it contains, the voluminous character of its bibliography, and the fair and unbiassed manner in which divergent theories are discussed.

THE TRANSLATORS.

LONDON; *November*, 1901.

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THE
CLINICAL PATHOLOGY OF THE BLOOD.

CHAPTER I.

METHODS OF INVESTIGATION.

In the following pages I shall briefly mention and explain the methods, other than bacteriological or chemical, which are usually employed in an investigation of the blood.

I. ESTIMATION OF THE VOLUME OF THE BLOOD.—The methods which up to the present time have been employed to estimate the volume of the blood are not accurate, and it is probable that the limits of error exceed the physiological and pathological variations of the volume. Further, the necessary details are so minute that it is impossible to use these methods for clinical purposes.

1. *Valentin's method* (1).—The volume of blood = x. A specimen of blood is taken from a living individual, evaporated and weighed. This residue = a per unit of volume. A measured quantity, c, of distilled water is injected into the veins, and a second specimen of blood is taken and estimated as before. The second residue = b per unit. The total amount of solids in the first specimen of blood is a x, in the second b (x + c). If we assume that the injected water remains in the blood-vessels, these values must be equal, and therefore—

$$x = \frac{b\,c}{a - b}$$

This assumption, however, is not permissible, as the fluid injected into the veins is rapidly absorbed ; consequently the method is not reliable.

2. *Vierordt's first method* (2).—The entire quantity of blood in the body passes through the left ventricle during its circulation. We are, therefore, able to estimate the volume of the blood if we know (a) the time of one complete circulation, (b) the number of contractions made by the ventricle during this time, (c) the amount of blood pumped out by the left ventricle at each contraction. Vierordt estimated the time of the complete circulation at 23·1 seconds, and the amount of blood thrown into the circulation by the contraction of the left ventricle at 172 c.c. The volume of blood, then, in an average man weighing 63·6 kg. would be 4760 c.c., that is to say 5020 gr., or about $\frac{1}{13}$ of the body-weight. This method is obviously too uncertain to be of clinical value.

3. *Vierordt's second method* (3).—This is a little more reliable. A measured quantity (a) of blood is taken, and the number (b) of red blood-corpuscles in it estimated. The same quantity of blood is again withdrawn after such an interval that, although sufficient time has not been allowed to elapse for the number of red corpuscles to be restored to the normal, the fluid removed in the first specimen shall have been replaced. Let the number of red corpuscles in the second specimen = c. Now if x be the volume of blood, we have the equation—

$$x = \frac{a\,c}{b - c}$$

Mallassez, using this method in the case of a man who was being bled for the benefit of a patient, found that the relation of the volume of the blood to the body-weight was as 1 : 9·33.

4. *Buntzen's method* (4).—A drop of blood is taken from the finger and the number of red corpuscles in it counted. A measured quantity of blood is now removed from a vein, and the number of red corpuscles in successive drops taken from the finger estimated until the number reaches its minimum. The calculation is then made by means of the above

formula. No great clinical or practical value can be claimed for this method, as it is necessary to assume that the volume of blood has returned to the normal when the number of red corpuscles has reached its minimum.

5. *Thibaut's method* (5).—Arterial blood contains about 18 per cent. of oxygen, venous blood about 8 per cent.: venous blood must, therefore, absorb about 10 per cent. of oxygen, and 100 volumes of blood are required to take up 10 volumes of oxygen. At every deep inspiration about 66 c.c. of oxygen are absorbed, consequently 660 c.c. of venous blood become arterial, and as there are eighteen respirations per minute, 660 c.c. of blood become arterialised in 3·3 seconds. Now the complete circulation of the blood takes about twenty-three seconds, therefore the total volume of blood is $\frac{660 \times 23}{3·3}$ or 4600 c.c. If we take the specific gravity of the blood as 1060, the weight of the blood will be about 4876 gr. Hitherto the weight of the blood of an average man has been taken at $\frac{1}{13}$ of the body-weight, that is 5 kg The above method, although ingenious, is not sufficiently accurate to be of clinical value.

II. ESTIMATION OF THE RELATIVE VOLUME OF BLOOD-CORPUSCLES AND PLASMA IN BLOOD.—This question of relative volume is important chiefly because by means of it we are able to obtain the respiratory surface of the blood, but also because we gain some insight into the chemistry of the blood. Welcker, Hoppe-Seyler, Bunge, and those of A. Schmidt's school tried many more or less complicated methods in the course of their physiological investigations for estimating the amount of plasma in a given specimen of blood, and C. Schmidt has published the results of similar investigations made from the clinical point of view. These methods are extremely tedious, and can never be of clinical value.

1. *Method of Blix-Hedin* (6).—Hedin suggested the use of centrifugal force, and constructed the following apparatus.

This apparatus (Fig. 1) consists of a capillary tube in which a measured quantity of blood is mixed with Müller's fluid or some similar solution, and of two small tubes (*a*, *a*)

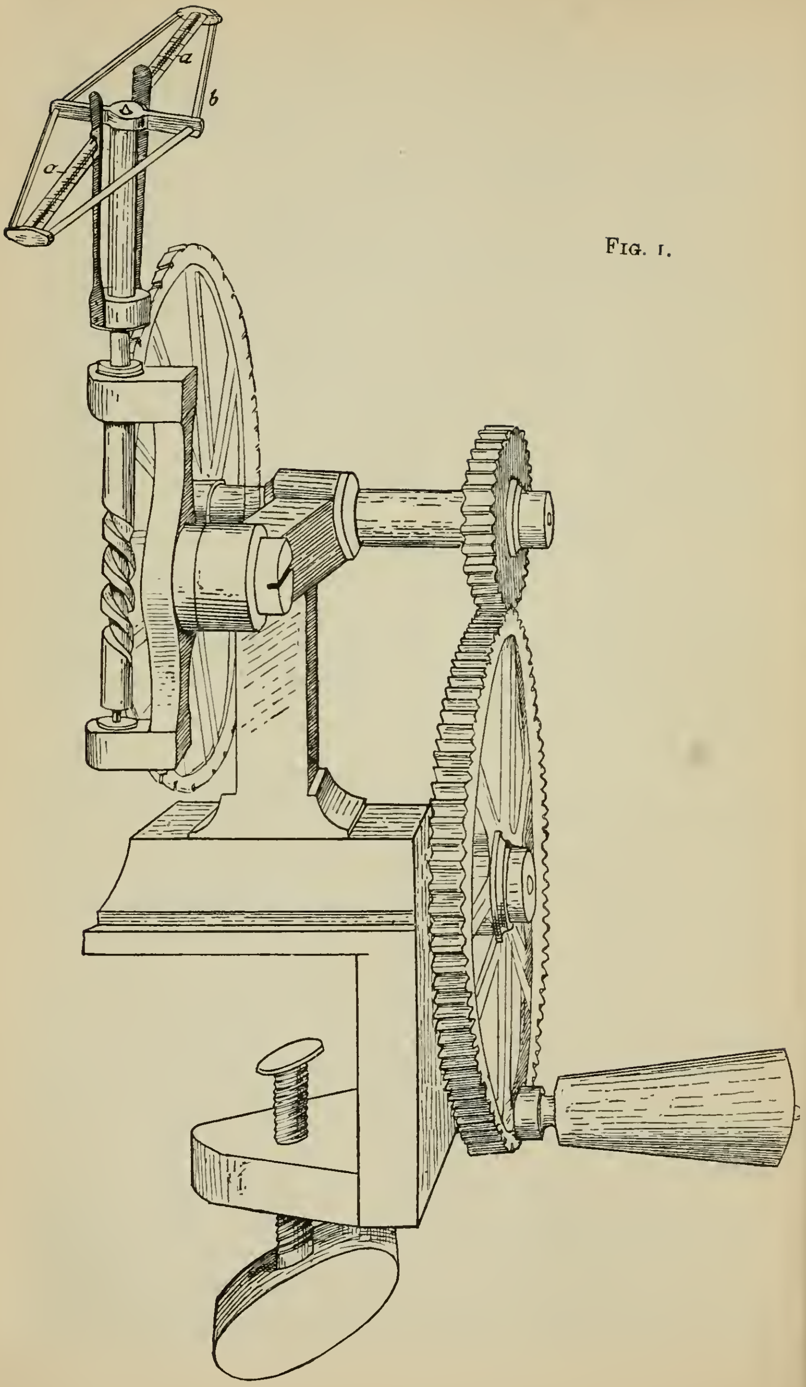
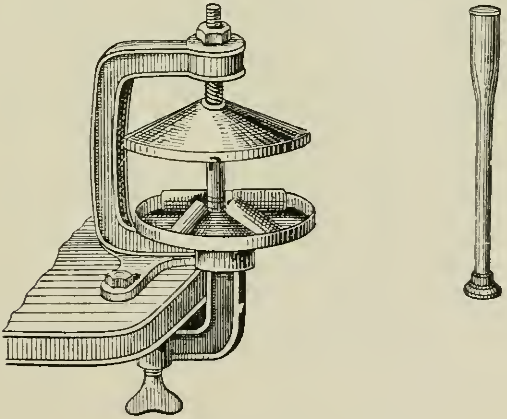


Fig. 1.

35 mm. long, and with a lumen of 1 sq. mm. These latter tubes fit into a metal frame (*b*) in such a way that each lies in one of the acute angles, where it is closed by a small india-rubber cushion; the frame is placed on a centrifugal machine capable of making 9000 rotations per minute. In making an experiment, a small quantity of blood is mixed in the capillary tube with an equal quantity of Müller's fluid, and then transferred by suction to the two small tubes, which are placed in the centrifugal machine. The corpuscles separate from the plasma after being rotated for five minutes, the white corpuscles being internal to the red. The small tubes are graduated in such a way that by reading the numbers opposite these divisions in the tube, and multiplying by four, we arrive at the volume of corpuscles in 100 parts of normal blood.

Gärtner (7) has made certain improvements in this method. His apparatus (Fig. 2) consists firstly of a capillary pipette, with a capacity 0·02 c.c., which is filled with blood from the finger by means of a screw; and secondly, of a "burette," or thermometer tube, 5 cm. long. One end of this is fused to a small glass funnel, the other end is closed by an india-rubber cap. The burette is graduated, the difference between the top and bottom of the scale being 0·02 c.c., or exactly the quantity of blood used. The blood

FIG. 2.



in the capillary pipette is transferred to the burette, and the corpuscles which adhere to the sides of the tube are also washed into the burette with some diluting fluid. The contents of the burette are mixed by means of a fine wire; the instrument is then placed in a small felt case, and connected with Gärtner's centrifugal machine; this is rotated for six minutes, and the percentage of corpuscles read off the scale. Gärtner uses a solution of potassium bichromate (8) as a diluting fluid.

Koeppe (9) simplifies this method by sucking the blood directly into a graduated pipette which he joins to a Pravaz syringe by means of an india-rubber tube. Rosin (10) makes a similar suggestion, but is not satisfied with his method or with his diluting fluid (25 per cent. of peptone in normal saline solution).

Another method for estimating the respective volumes of corpuscles and serum, known as the "sedimentation" process of Biernacki (11), is similar to this centrifugal method, but requires a much larger quantity of blood. Blood which has been defibrinated or mixed with sodium oxalate to prevent the formation of clots, is allowed to stand in a tall glass cylinder for twenty-four to forty-eight hours. The height of the sediment of the fluid is then measured and the respective volumes estimated.

Bleibtreu's method (12) appears to be the most accurate yet proposed. In this certain quantities of blood, b_1 b_2, are diluted with known quantities, s_1 s_2, of normal saline solution. After the corpuscles have settled, the clear superincumbent fluid is drawn off and the amount of nitrogen in it estimated by Kjeldahl's method. Taking the amounts of nitrogen as n_1 n_2, the brothers Bleibtreu found, after many experiments, that the formula $x\ (n_1 - n_2) = n_2\frac{s_1}{b_1} - n_1\frac{s_2}{b_2}$ represents the volume of the serum.

In their early experiments the brothers Bleibtreu used concentrated saline solutions as their diluting fluids, but in their later experiments they replaced them by 0·6 per cent. solution of sodium chloride, the so-called physiological saline solution, on the assumption that the red corpuscles would remain intact. The value of the method rests on this assumption. Hamburger (13) states that normal saline solution is not an inert fluid as far as the corpuscles are concerned, and that no fluid can be inert in this particular unless it has the same osmotic tension as the serum of the blood which is investigated. Ejkmann (14) supports Hamburger, and points out that the volume of the corpuscles is smaller after treatment with normal saline solution than it is when more concentrated solutions are employed. I have made repeated experiments on this point, and my results fully confirm Ejkmann's statement. Serum which has been diluted with saline solution absorbs nitrogenous bodies from the blood-corpuscles; and as the amount of these bodies varies with the isotonic value of the solution, we obtain contradictory results. Again, we can readily observe by means of the microscope how concentrated solutions lead to contraction of the corpuscles. This all agrees with what I pointed out some time before Ejkmann's paper appeared, viz. that it is impossible to rely on the results obtained from different specimens of blood on account of the variations in the isotonic value of the red corpuscles. Hamburger's recommendation that we should use a salt solution isosmotic with the serum, is full of difficulties, as it takes a considerable time to estimate osmosis, and during this time the osmotic value of the serum is considerably altered by the breaking down of the corpuscles.

It is clear, then, that none of our present methods of estimating the respective volumes of the serum and corpuscles are reliable or accurate.

Example of the blood-analysis of a case of chlorosis: S. Marie, November 9th, 1894. Blood from vein defibrinated.

Isotonic value	0·38 per cent. NaCl
Specific gravity of the blood . . .	1035
,, ,, serum . .	1021
Red corpuscles in mm.^{3}.	3.120,000
Nitrogen of blood	1·974 vol. per cent.
,, serum	0·7896 ,, ,,
,, diluted serum . . .	0·3444 ,, ,,
Sodium chloride of blood . . .	0·5148 ,, ,,
,, serum . . .	0·5967 ,, ,,
Dry residue of the blood . . .	12·78 per cent. of weight
,, serum . . .	7·06 ,, ,,

Calculation.

100 gr. blood = 96·61 c.c.
100 „ serum = 97·94 „
Vol. of serum = 77·35 per cent.
„ corpuscles = 22·64 „
„ 1 corpuscle = ·0000000725 c.c. = 725 C.mm.^{3}
In 100 c.c. blood—
In the serum 0·6108 gr. N_2 and 0·4616 gr. NaCl.
In the corpuscles 1·3632 gr. N_2 and 0·0532 gr. NaCl.

In 1 corpuscle, 43·6 C.mgr. N_2 = 6·0 vol. per cent. = 5·5 per cent. weight.

In 1 corpuscle, 1·7 C.mgr. NaCl = 0·23 vol. per cent. = 0·21 per cent. weight.

In 100 c.c. blood, 13·22 gr. dry substance and 90·28 gr. H_2O.
„ serum, 7·20 „ „ and 94·90 „ „
In 100 c.c. blood—
In serum, 5·56 gr. dry substance and 73·41 gr. H_2O.
In corpuscles, 7·66 „ „ and 16·87 „ „

One corpuscle, therefore, contains 245 C.mgr. dry substance = 33·7 vol. per cent. = 31·2 weight per cent., and 540 C.mgr. H_2O = 74·6 vol. per cent. = 68·8 weight per cent.

Weight of 1 red blood-corpuscle, 785 C.mgr.

Specific gravity of 1 red blood-corpuscle, 1082.

III. The examination of the cellular elements of the blood.—(*a*) *Enumeration of the corpuscles and platelets.*—All the methods suggested for this purpose depend upon the determination of the number of blood-corpuscles in a very small portion of blood, which has been uniformly mixed with some preserving fluid. The number of such fluids is very large, as any fluid can be utilised which contains a certain amount of salt in so-called isotonic concentration. The addition of an aniline dye to one of these fluids has the advantage of rendering the white corpuscles more distinct; but on the other hand, the dyes often form sediments, so that repeated filtration is necessary to prevent the apparatus used from becoming dirty. The following fluids are recommended for use in counting the red corpuscles:

Pacini's solution:

Mercuric perchloride . .	2·0
Sodium chlorate . .	4·0
Glycerine . . .	26·0
Distilled water . .	226·0

One part to be mixed with three of water before use.

Hayem's solution :

Mercuric perchloride	0·5
Sodium sulphate	5·0
Sodium chlorate	1·0
Distilled water	200·0

Gowers' solution :

(1) Sodium sulphate	6·3
Acetic acid	3·6
Distilled water	117·0

(2) A water solution of sodium sulphate of sp. gr. 1025.

Potain's solution :

Equal volumes are taken of solutions of gum arabic, sodium sulphate, and sodium chloride, all of sp. gr. 1020.

Mosso's solution :

Osmic acid	1
Distilled water	100

Mayet's solution :

Neutral sodium phosphate	2·0
Distilled water	100·0

Add cane-sugar until sp. gr. is 1085.

Löwit's solution :

Sodium chlorate	2·0
Sodium sulphate	4·0
Mercuric perchloride	4 c.c. (sat. sol.)
Distilled water	300·0

Toisson's solution :

Glycerine	30 c.c.
Pure sodium sulphate	8 gr.
Sodium chloride	1 gr.
Methyl violet, 5 B.	0·025 gr.
Distilled water	160 c.c.

This fluid stains the nuclei of the white corpuscles.

Gräber's method :

Magnesium sulphate	5·0
Distilled water	100·0

Mallassez' method :

Solution of urea sp. gr. 1020—1024, containing 5—6 per cent. of sodium sulphate.

It is necessary to use a fluid which preserves the white cells but breaks up the red corpuscles, if we wish to estimate the number of white blood-corpuscles in a satisfactory manner. The best fluid for this is a 0·3 to 0·5 per cent. solution of acetic acid (Thoma), to which a small quantity of an aniline dye may be added.

It is usual (Klein, 17; Müller and Rieder, 18) in making a differential count of the white corpuscles to form an estimate of the relative proportion of the different white cells in a dried microscopic specimen, and then to calculate the actual numbers from an enumeration of the total number of white corpuscles made in the ordinary way. Eltzholz (19) uses solutions which stain the granular forms of white corpuscles. These solutions are as follows:

(*Solution A.*)

Eosin 2 per cent.	7 parts.
Glycerin	45 ,,
Distilled water	55 ,,

(*Solution B.*)

Concentrated aqueous solution of gentian violet	5 or 6 drops.
Alcohol	1 drop.

Blood is drawn up a Thoma-Zeiss white corpuscle pipette to the mark 1 or 1·5, and then solution A until half the bulb is filled. The bulb is well shaken for three or four minutes and the solution B sucked up until the mark is reached. The different stained cells can now be readily counted under the microscope.

Zappert's (20) *method for counting the eosinophile cells.*—Four or five drops of a filtered mixture of 10 parts of water, 10 parts of glycerin, and 5 parts of a 1 per cent. aqueous solution of eosin are added to 5 c.c. of a freshly made solution of osmic acid; the resulting mixture is well shaken, and then used as the diluting fluid in a Thoma-Zeiss pipette. The same instrument can be used for the red and the white cells, but as the latter are comparatively few in number, the blood is diluted to a less extent in their estimation; thus in counting the red cells the blood is diluted 100 to 200 times, in counting the white cells ten to twenty times.

The same instrument which is used to estimate the number of white cells is employed in counting the blood platelets. Among the fluids used for this purpose the following may be mentioned:

Pruss's (24) solution:
  10 parts of 1 per cent. solution of chromic acid.
  10 parts of 1 per cent. solution of osmic acid.
  1 part of glacial acetic acid.

Affanasiew's (25) solution:
  0·6 per cent. solution of sodium chloride.
  0·6 per cent. solution of peptone, together with a little methyl violet.

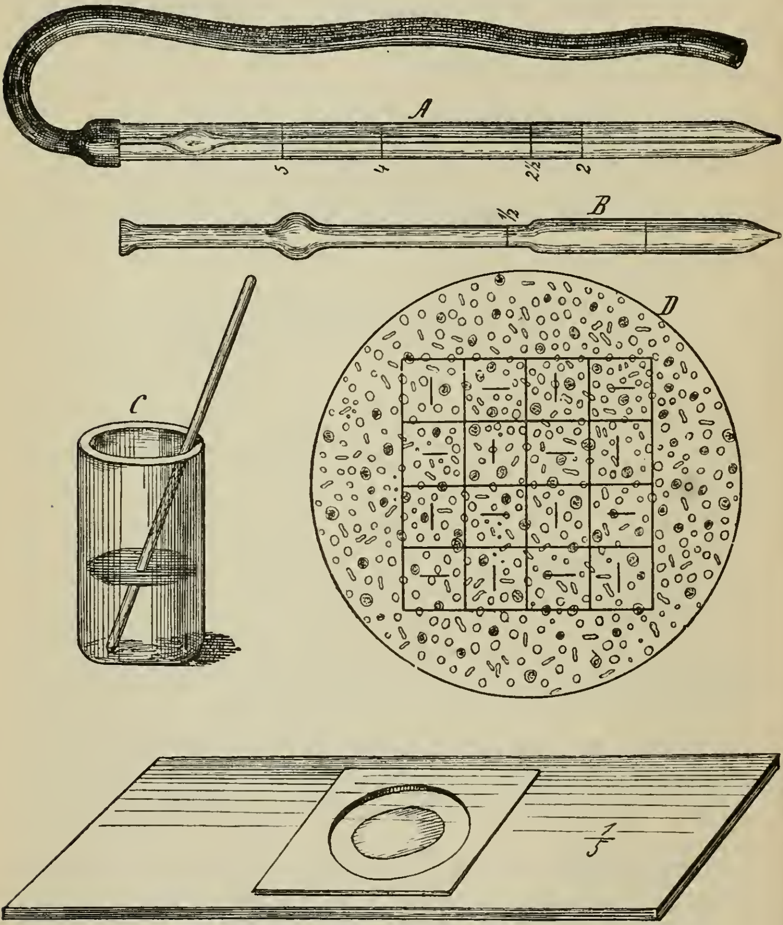
Hayem recommended diabetic urine. The platelets are difficult to count, as they tend to adhere to one another. Affanasiew attempted to prevent this by adding peptone to his solution.

Among the instruments now in use for the purpose of counting the blood-cells the following may be mentioned:

1. *Hayem's apparatus* (26).—This consists of two pipettes (*A* and *B*), a small vessel and mixing rod (*C*), a specially constructed slide (*E*), and a microscopic eyepiece which is divided into squares. The pipette *A* is graduated for 2, 2·5, 3, 4, and 5 mm., and has an india-rubber tube and mouthpiece attached at one end. *B* is similar, but has a capacity of 500 mm.: *C* is about 2 cm. high and has a flat bottom: the slide *E* has a glass slip $\frac{1}{5}$ mm. thick, with a circular piece 1 cm. in diameter cut out of its centre superimposed upon it; whilst a small disc divided into sixteen small squares, which form one large square, is inserted into the microscope.

Two cubic millimetres of blood are drawn up into the pipette *A* and blown down into and thoroughly mixed with 5 c.c. of the preserving fluid previously placed in the receiver *C*. A drop of the fluid is placed on the slide and covered with a strong cover-slip. On looking through the microscope the field of view is seen as in Fig. 3, *D*. Each side of the square is $\frac{1}{5}$ mm. in length, therefore the cubic contents of the counting space is $\frac{1}{125}$ c.mm. The number of corpuscles in a cubic millimetre is therefore = (the number in a square) × 125 × (the amount of dilution). This

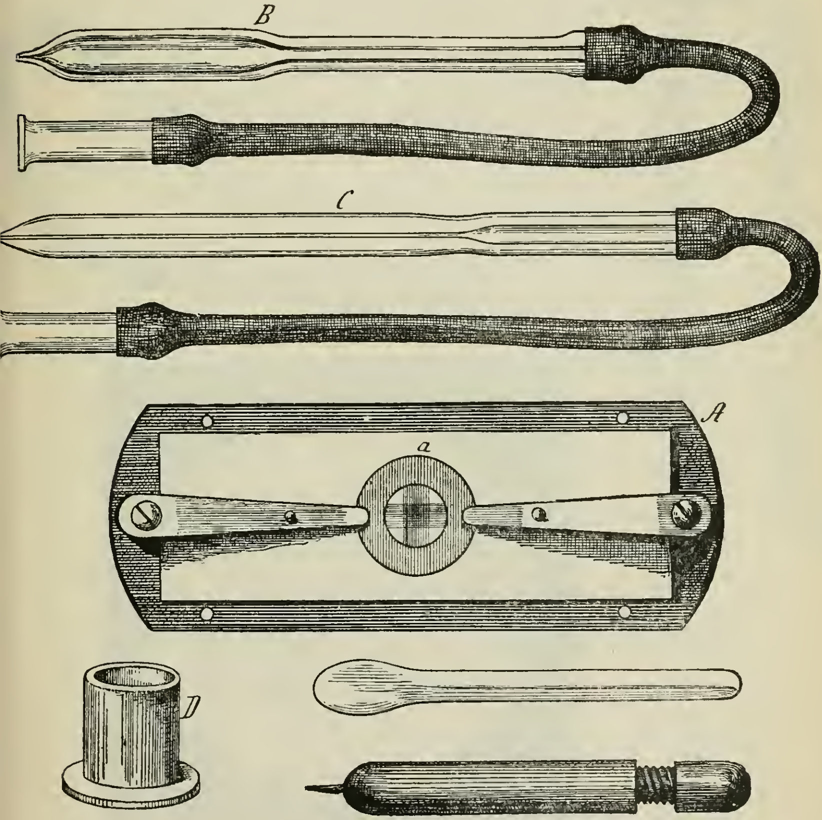
FIG. 3 (Hayem).



should be 2 : 500, but as it is assumed that 4 mm.^{3} stick to the sides of the tube *B*, it is taken to be as 2 : 496 or 1 : 248. Therefore we multiply by 125 × 248, *i. e.* by 31,000.

2. *Gowers' Hæmocytometer* (27). — This is similar to Hayem's apparatus. The square divisions are marked on the slide instead of being on the microscope; the side of a square is $\frac{1}{10}$ mm. instead of $\frac{1}{5}$; the depth is the same, viz. $\frac{1}{5}$ mm. The pipettes *B* and *C* contain 995 mm.^{3} and 5 mm.^{3} respectively, so that the number of corpuscles found in a square must be multiplied by 100,000 to get the number in one cubic millimetre of blood.

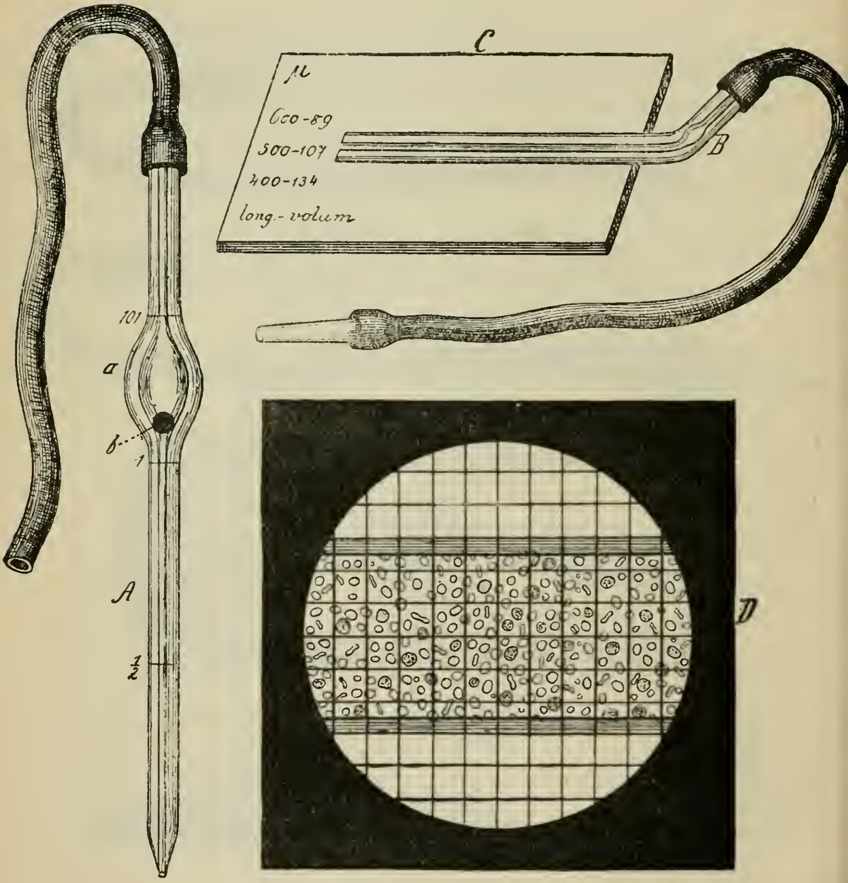
FIG. 4 (Gowers).



In this method, as in the last, the mistake of having a special receiver is made.

3. *Mallassez' apparatus* (28).—This is less convenient than the preceding. It consists of a capillary tube enlarging

FIG. 5 (Landois).



into an egg-shaped bulb (*A*) some way from the end. Below the bulb the tube is marked $\frac{1}{2}$ and 1, whilst above is the mark 101. The upper end is fitted with a rubber tube and mouthpiece. In the bulb is a freely moveable glass bead (*b*). There is a second capillary tube *B*, glued on to a slide *C*, with a rubber tube over its free end. On the slide the following figures are marked :

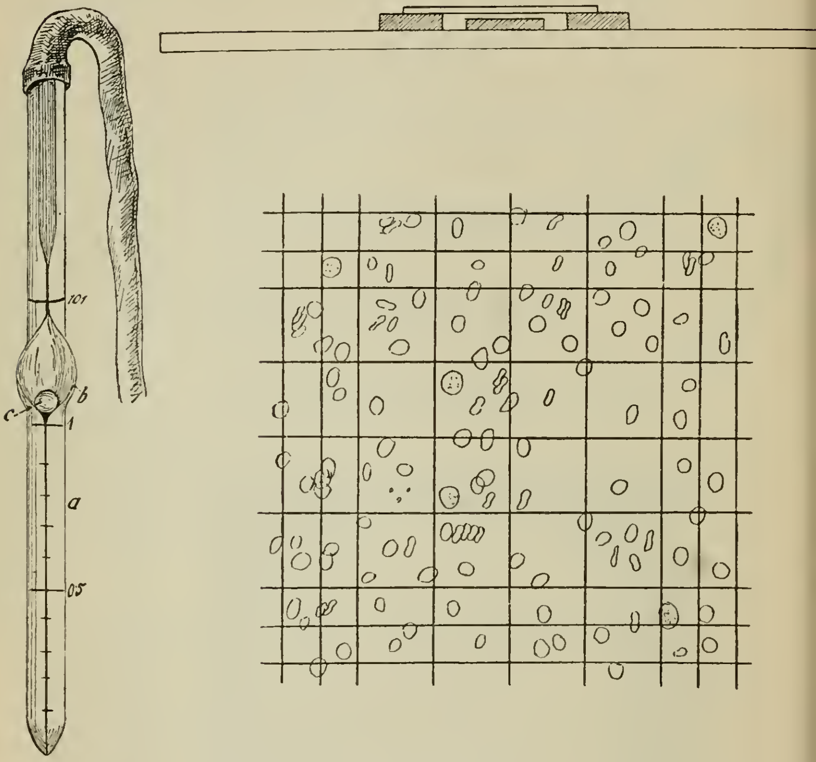
600	89
500	107
400	134

i. e. a length 600 μ of the tube contains 89 mm.^{3}, and so on. There is also an eyepiece containing a glass divided into one hundred equal squares (*D*). The apparatus is used as follows :—A scale divided into parts of $\frac{1}{100}$ mm. is placed on the stand of the microscope, and the tube is drawn out to such a distance that the sides of the squares of the eyepiece represent forty to sixty of them. A side of the square is therefore 400 to 600 μ in length. *A* is filled with blood up to mark $\frac{1}{2}$ or 1. Diluting fluid is then drawn up to 101, the bulb is shaken for two minutes to defibrinate the blood and to get a uniform mixture ; a few drops are now placed in front of the tube *B* and sucked up until about two thirds of the tube are filled, and the number of corpuscles in the field of view counted. According to the scale on the slide the cubic contents of the tube are known, and the calculation is obvious ; but as it is more complicated than in the other methods there is more room for error.

4. *Thoma-Zeiss's apparatus.*—This is a method based on those of Gowers and Mallassez. It consists of a capillary tube about 10 cm. long which enlarges into an ovoid bulb (*b*) in which there is a freely moveable glass bead. Below the bulb are the marks 0·5 and 1·0, whilst above is the mark 101. There is a counting space constructed after the model of Gowers, which consists of a glass frame, with a circle cut out, glued on to a slide ; in the basin so formed is a small circular glass disc with small squares engraved in its centre. The difference in height between the frame and the disc is exactly 0·1 mm., and the side of one of the squares is $\frac{1}{20}$ mm. The counting is done as follows :—Blood is sucked up to the mark 0·5 or 1 and the diluting fluid up to 101. The tube is then well shaken. A drop of the mixture is placed on the glass disc and a special thick cover-glass pushed over from the side. If the preparation is successful Newton's rings become visible. The preparation is then allowed to

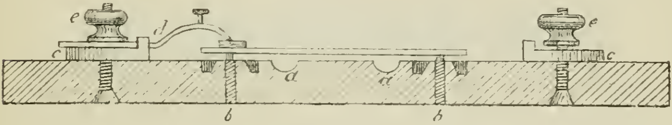
stand for one or two minutes so that the corpuscles have time to settle. The number of corpuscles may now be counted. A small square has a capacity of $\frac{1}{400}$ mm.^{3}, and sixteen of these small squares form a large one, which is marked off by parallel lines; it is best to count sets of four small squares, and naturally more accurate results are obtained when a large number of squares are counted. In counting the corpuscles in the rectangle formed by the four small squares, corpuscles lying on the left and base line must be omitted if the corpuscles which lie on the right and top lines are included.

FIG. 6.



The number of corpuscles per mm.^{3} is the number counted, multiplied by 4000, and by the amount of dilution, *i. e.* 100 or 200; and divided by the number of small squares counted, or four times the number of rectangles counted. Miescher (29) has made some alterations in the Thoma-Zeiss mixing pipette; he uses three principal marks, noting dilution of $\frac{1}{100}$, $\frac{1}{150}$, and $\frac{1}{200}$, together with auxiliary marks, so that if one of the principal marks is not exactly hit off, the difference can be estimated within $\frac{1}{500}$ part. Lederer (30) compared the results estimated by means of Miescher's and Thoma-Zeiss's methods, but found no appreciable difference.

FIG. 7.



5. *Alferow's hæmatocytometer* (31).—This apparatus consists of—

(1) A special counting chamber.

(2) A mixer (after Potain).

(3) A special needle.

(4) A dark chamber with two rough glass discs divided into squares.

(5) A micrometer reading up to $\frac{1}{100}$ mm.

The counting chamber consists of a slide of looking-glass (Fig. 7) 3 to 4 mm. thick, with two grooves of half its thickness, and from $\frac{1}{2}$ to 1 cm. apart, running across it. Three or four holes are bored near this groove, and small coloured glass tubes or micrometer screws of known height placed in them.

The cover-glass is placed on these pillars, and is kept down by two springs, one on each side. In this way the depth is known. When we wish to use the instrument the cover-glass is fixed, and then the prepared blood mixture is drawn between it and the slide by capillary attraction.

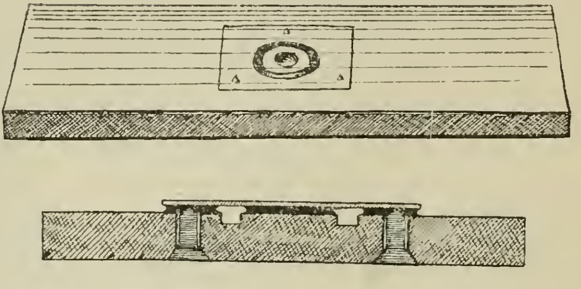
The method of counting is also original.

Alferow either takes a microphotograph or marks the corpuscles on the discs with a pencil in the dark chamber, and then counts on a glass disc marked in squares.

6. *Mallassez' new "counting chamber"* (32).—This consists of an ordinary slide in the middle of which a circular

groove, 15 mm. broad and 1 mm. deep, encloses a circle from 6 to 7 mm. in diameter. Three or four screws of very low pitch are placed near the groove, so that they show the height above the slide. The drop of blood mixture is placed on the central circle, whilst a drop of water is placed on the slide outside the groove to prevent evaporation. Care must be taken that the cover-glass projects beyond the screws. The centre of the slide is graduated in rectangles $\frac{1}{4}$ mm. by $\frac{1}{5}$ mm., so that if the height of the screws is $\frac{1}{5}$ mm. the cubic content of a rectangle is $\frac{1}{100}$ c.mm.; and as there are ten groups of ten of these rectangles, each group represents a volume of $\frac{1}{10}$ c.mm. The calculation is consequently simple. This new apparatus of Mallassez has the further advantages of being easy to clean and of not being readily broken. The whole apparatus consists of—

FIG. 8.



(1) A needle.

(2) A mixer (after Potain), the tube of which is $\frac{1}{100}$ part of the bulb, and graduated so that we can get dilutions of $\frac{1}{100}$, $\frac{2}{100}$, $\frac{3}{100}$, $\frac{4}{100}$, and $\frac{5}{100}$.

(3) A bottle of diluting fluid.

(4) A "chambre humide."

(5) A "compressor," *i. e.* a small apparatus to keep the cover-glass on the screws.

The errors in all these methods are due to inaccuracy in taking the blood, in measuring and diluting, in dropping the right amount of fluid on the slide, in counting, in the apparatus, and in unequal mixture of the blood and fluid. These errors, often mentioned by authors, have been specially studied by Reinert (33). In taking the blood it is obviously necessary to avoid all pressure upon the finger. Reinert, for instance, counted 4,582,000 red corpuscles in one case, and then waiting a little and pressing the finger found only 3,860,000 cells. It is obvious that inaccuracies in the withdrawal of blood and the measuring of diluted fluid are of the greatest importance. Care must be taken that the cover-glass rests as closely as possible on the slide, so that we know the correct depth of the fluid, whilst the instrument itself must be correctly graduated. For this purpose, as we have seen, Alferow and Mallassez have two specially constructed compressors with springs. Alferow used microphotography to avoid errors in counting.

The errors due to the instruments themselves are not inappreciable. Heyl found a difference of 25 per cent. on comparing a Thoma-Zeiss with an old apparatus of Mallassez. Laache (34), using Hayem's apparatus, found 18 per cent. less than when he followed Mallassez' method. Thoma (35) examined five Zeiss instruments with the same specimen of blood, but found hardly any appreciable difference; this was still further reduced by taking the average of his results. In 61,000 cells it only amounted to 0·32 per cent., which speaks volumes for the accuracy of the Zeiss instruments.

To see how many cells ought to be counted to obtain reliable results, Lyon and Thoma counted one hundred squares, using a dilution of 1 in 200 in twenty-four preparations of a specimen of blood, and found, in an average of 1141 cells, a variation of 1·82 per cent. In another case, with an average of 934 cells, there was a variation of 2·71 per cent. Reinert obtained similar results. It follows, therefore, that we must count at least 1000 cells if we wish to obtain anything like a reliable result.

(*b*) *The histological investigation of the blood-corpuscles.*—We can examine the condition of the blood-cells either in a fresh preparation or in dried specimens. In the examination of fresh blood it is often sufficient—as, for instance, in the diagnosis of an obvious case of leukæmia—to place a drop of the suspected blood on a slide, cover it with a cover-slip, and examine it under the microscope. This method is especially useful in cases of malaria and recurrent fever. It is necessary, however, to adopt certain precautions; thus evaporation must be prevented, either by placing a layer of vaseline round the cover-slip, or by some other means. In dealing with the blood of malaria it is best to use a warm stage, but in examining for the spirilla of recurrent fever I prefer a hanging drop of the blood. As a rule an examination of the fresh blood is not sufficient, and we have to examine dried specimens. Ehrlich (36) and his pupils discovered that certain drying methods not only did not alter the appearance of the red and white cells, but kept their structure defined; they also showed that certain empirical relations existed between the cells and a variety of aniline dyes.[1] Ehrlich divides the aniline dyes into three groups, acid, basic, and neutral. The first group contains those in which the colouring principle is an acid, such as picrate of ammonia. The members of this group are again subdivided according to their reaction with the α granules of the white cells (see below). For the first subdivision we have—

(1) The fluorexins (tetrabromfluorexin = eosin).

(2) The strongly acid nitrogenous bodies (*e. g.* "Martius yellow," a salt of binitro-naphthol)—the picric acid salts or the "aurantia" (hexanitro-diphenylamin).

(3) The "sulphur acids" (rosanilin, malachite green, methyl violet, indulin, bengalin, nigrosin, tropæolin, bordeaux, ponceau). The second subdivision contains—

(1) Fluorexin and chrysolin.

(2) Picrate of ammonia and "naphthylamin yellow."

(3) Orange and real yellow.

The *basic* dyes contain a combination of a colouring base and an indifferent acid, *e. g.* acetic rosanilin (= fuchsin) and its derivatives, bismarck brown, safranin, scarlet, methyl green, and methylene blue.

The *neutral* consist of the combination of an acid dye with a basic, *e. g.* picrate of rosanilin, a combination of ammonia picrate and acetic rosanilin. This division was made by Ehrlich on the ground that the tissues had different affinities for the dyes, and that they always picked out certain particular colours from a mixture of different dyes. Ehrlich in this way distinguishes between acid (or eosinophile), basic, and neutrophile cells and granules.

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[1] Benares ('Deutsch. med. Woch.,' 1894, p. 572) recommends formol for fixing blood preparations. A small quantity of a 10 per cent. solution of formol is diluted with nine times its amount of alcohol; the preparations are immediately placed in this solution, kept there for one minute, and then, without drying, transferred to the staining mixture (eosin hæmatoxin)

A dried and stained blood specimen is made as follows (Ehrlich) :—A drop of blood is pressed between two cover-slips so that each retains as thin a layer as possible. The dried preparation is heated on a copper plate at a temperature of 110° to 130° C. for ten to twelve hours, in order to fix the hæmoglobin of the red cells. Nikiforoff (37) and Gabritschewsky (38) fix the hæmoglobin by placing the specimen for twenty minutes in a solution consisting of equal parts of ether and alcohol. When the hæmoglobin has been fixed the cover-glass is placed, with the blood specimen on the lower side, in a mixture of acid, basic, and neutral dyes. The mixtures proposed for this purpose are numerous.

Ehrlich's triacid mixture :

Saturated water solution of orange G.	125	c.cm.
,, ,, of acid fuchsin containing 20 per cent. alcohol	125	,,
Add, whilst stirring, conc. aq. solution of methyl green	125	,,
And absolute alcohol	75	,,

Ehrlich's new mixture (39) :

Conc. aq. solution of orange G.	120—135	c.cm.
,, ,, of acid fuchsin	80—165	,,
,, ,, of methyl green	125	,,
Add water	300	,,
,, abs. alcohol	200	,,
,, glycerine	100	,,

These mixtures show up all the known granulations, especially the ε granules. The latter mixture stains rapidly —in about two minutes.

Schwarze's mixture (40) :

Saturated solution of aurantia in glycerine	1 vol.
Pure glycerine	1—2 vols.

Eosin and aniline black in excess.

This is especially useful to show up the *a* granules.

Gollasch's mixture (41) :

Eosin cryst.	15 gr.
Hæmatoxylin	2 ,,
Distilled water Absolute alcohol Pure glycerine	āā 100 ,,
Glacial acetic acid	10 ,,
Alum	in excess.

This mixture should be exposed to the light for three weeks; it then becomes dark blue-black. It stains slowly, but produces very fine pictures, and is especially useful for showing the figures produced by the segmentation of cell nuclei.

Huber's mixture (42) :

Aurantia Indulin Eosin	āā 2
Glycerine	30

Plehn's mixture (43) :

Conc. aq. solution of methylene blue	60 c.cm.
½ per cent. of eosin in 75 per cent. alcohol	20 ,,
Distilled water	40 ,,

Add twelve drops of 20 per cent. solution of caustic potash.

Fix the preparation in absolute alcohol (three to five minutes), and stain for five to six minutes in the cold. This mixture colours the eosin granules and malarial parasites extremely well. It must be filtered before use.

Aldehoff's method (44).—The preparations are allowed to lie for half an hour in a concentrated alcoholic solution of eosin (cold), or for two to three minutes in a warm solution, then washed with water and placed for one minute to one minute and a half in a concentrated aqueous solution of methylene blue.

The results are similar to those obtained by Plehn's method.

Gabritschewsky's method (45).—Let the preparation dry in the air. Treat for five minutes with a mixture of equal parts of ether and alcohol, then place for five minutes in a 1 per cent. alcoholic solution of eosin. Wash with water and then allow a drop of concentrated aqueous solution of methylene blue to remain upon the cover-glass for one minute.

This is the quickest method, and gives just as good results as Plehn's, but failure often occurs from unknown causes. Malarial parasites, neutrophile and eosinophile granules, are well stained by it.

Feletti's stain (46).—A drop of 2 per cent. alcoholic solution of methylene blue is allowed to evaporate on the slide. The cover-slip, with the fresh film of blood, is placed on the residue. The preparation is fixed with paraffin. The white corpuscles, platelets, bacteria, and malarial parasites are said to be coloured by this method.

Ehrlich's method of colouring basophile granules :

Saturated alcoholic solution of dahlia . . .	50 c.cm.
Glacial acetic acid . .	10—20 ,,
Distilled water . . .	100 ,,

Westphal's method for colouring all the granules (47).—100 c.cm. solution of carmine after Grenacher's method (carmin. pur. 20, aq. dest. 200, alum crud. 5) are boiled, filtered, and diluted with 1 gr. of carbolic acid. Glycerine 100, concentrated alcoholic solution of dahlia 100, and glacial acetic acid 20, are then added. This method of staining takes twenty-four hours at the ordinary temperature.

Rieder (48) follows Härtung, and uses ether-alcohol, and then eosin, glycerine, and hæmatoxylin in two stages.

Chenzinsky's solution (49):

Conc. aq. solution of methylene blue .	40 vols.
½ per cent. solution of eosin in 70 per cent. alcohol . . .	20 ,,
Glycerine	40 ,,

Klein's mixture (50):

Methylene blue . . .	3
Aq. font.	100
Alcohol	5
Mix, and then add eosin (aq. solution)	·5

This solution is placed in a glass bottle, closed by a rubber cork, and left for some hours in an oven. It is advisable, after a week or two, to add a few drops of alcohol before using the mixture.

The staining is done as follows: a few cubic centimetres of the mixture are warmed in a watch-glass until the steam begins to rise; the preparation (fixed either by heat or by ether-alcohol) is placed in it for half a minute; it is then washed with water, dried, and mounted.

Romanowsky's method of staining for malarial parasites (51) is equally useful for other purposes:

Conc. aq. solution of methylene blue .	1 part.
1 per cent. aq. solution of eosin . .	2 parts.

The mixture must be made immediately before use, and should not be filtered. The older the methylene blue the better the stain.

Mannaberg (52), for malarial parasites:

Concentrated aqueous solution of methylene blue	40
2 per cent. solution of eosin in 60 per cent. alcohol . . .	80
Water	40

Dry preparations are very useful for showing the finer nuclear structure and segmentations of the leucocytes or nucleated blood-corpuscles. As in the case of the tissues it is advisable to use either 1 per cent. osmic acid, Flemming's fluid, picric acid, chromic acid, or sublimate. Of these Flemming's chrom-osmic mixture is the most useful, especially if the preparation is subsequently stained with safranin.

R. F. Müller employed a $\frac{1}{6}$ per cent. solution of chromic acid and then stained with safranin. This author recommended picric acid as especially suitable for showing nuclear mitosis. The heated dry preparation is placed for twenty-four hours in a saturated aqueous solution of picric acid and then washed for one hour in running water. It is next placed either in a very dilute solution of hæmatoxylin (Böhmer) for two to twenty-four hours, or in a concentrated solution of ammonia or boracic carmine. If the hæmatoxylin preparations are overstained they can be partly decolourised by treating them for a few seconds with $\frac{1}{4}$—$\frac{1}{2}$ per cent. hydrochloric acid solution of alcohol.

Mannaberg gives the following method for the detailed study of malarial parasites: the dry preparation is allowed to float for five minutes in distilled water, and is drawn repeatedly through a very dilute solution of acetic acid until all the hæmatoxylin is given up. The preparation is then placed for two hours in the following mixture:

A concentrated aqueous solution of picric acid	30
Distilled water	30
Glacial acetic acid	1

It is then left for two hours in absolute alcohol, and is subsequently stained for twelve to twenty hours in alum-hæmatoxylin in the cold.

Hæmatoxylin	10
Absolute alcohol	100

One part of this solution is mixed with two parts of a $\frac{1}{2}$ per cent. solution of ammonia alum just before the mixture is to be used; when the preparation has been sufficiently stained it is passed through a mixture of ·25 per cent. hydrochloric acid and 75 per cent. alcohol, a mixture of ammonia and alcohol (three drops of ammonia in 10 c.cm. of 75 per cent. alcohol); it is then washed in 80 per cent. alcohol, dried, and mounted.

The following methods are also recommended for special investigations:

Weiss's method (53) to show the furfurol reaction of the eosinophile granules: the preparations, fixed at 150° C., are placed for twenty-four hours in a 1 per cent. alcohol solution of vanillin. A few drops of the following ferric sulphate-sulphuric acid mixture are then placed on the cover-glass. Equal parts of chemically pure sulphuric acid and water are mixed, just before use, with a few drops of a solution of ferric sulphate. The edges of the cover-slips are fixed with Du Bois' cement. The eosinophile granules appear blue-black.

Gabritschewsky's method of showing glycogen:

Pure iodine	1
Potassium iodide . . .	3
Distilled water . . .	100
Gum Arabic . . .	in excess.

The dried preparation is placed in this solution for a few minutes. Many white corpuscles are thus stained a mahogany-brown colour. This Gabritschewsky and Lievierato considered to be due to the presence of glycogen; it is, however, probably due not to glycogen but to an amyloid antecedent (Czerny).

Neusser (55) recommended that the dried preparation should be stained with the following modified triacid solution in order to show the so-called *perinuclear basophile granules* in the white cells:

Concentrated aqueous solution of acid fuchsin .	50 c.cm.
,, ,, ,, of orange G. .	70 ,,
,, ,, ,, of methyl green	80 ,,
Distilled water	150 ,,
Absolute alcohol	80 ,,
Glycerine	20 ,,

Bremer (56) has lately published a new method of investigation which depends on the different relations of normal and pathological blood towards an eosin and methyl blue mixture. He prepares this mixture from a $\frac{1}{2}$ per cent. water solution of eosin and a concentrated water solution of methyl blue. The one has an excess of eosin and stains filter-paper reddish; the other has an excess of methyl blue and stains filter-paper blue. Both must be well stirred in small dishes. The preparations are dried after Ehrlich's method, and then placed successively in eosin and methyl blue. In normal blood the red corpuscles are coloured brown-red with a light central zone, the platelets and the nuclei of leucocytes are variously stained from violet to pure blue, the eosinophil granules are stained violet-red; the nuclei of the large and medium-sized lymphocytes are light blue, their protoplasm being generally dark blue; the small lymphocytes have, on the other hand, light blue protoplasm and dark blue nuclei, whilst the dried plasma is for the most part a faint red-blue.

According to Bremer, the relations of the cells are altered in true diabetes and glycosuria of different kinds, so that the blood-corpuscles remain unstained or take on a yellow or greenish-yellow staining, whilst the plasma appears colourless or pink. It is a striking fact that in diabetes the red cells remain refractory to eosin only, and not to other acid dyes, such as scarlet, aurantia, and fuchsin.

(*c*) *Measurement of the resistance of the red corpuscles to external injuries.*—The first two methods given here are based on the facts that the colouring matter (hæmoglobin) of the blood, which under physiological conditions remains within the corpuscles, immediately leaves them when they are brought into contact with distilled water; whilst, on the other hand, the hæmoglobin does not pass out of the cells if salt solution of a certain strength is used instead of water. In this way we can determine, for different salts (and also for different kinds of blood), the strength which is just necessary to counterbalance the "hæmoglobin-loosening" effect of water. Such a solution was called by Hamburger "isotonic."

The following methods are recommended for estimating the strength of an isotonic solution:

(1) *Landois' method* (57).—Mix a drop of blood with an equal quantity of 3 per cent. saline solution, and add water under the microscope until the corpuscles begin to dissolve. In this way we find the strength of the blood in salts and especially sodium chloride, which is just under Hamburger's isotonic concentration.

(2) *Hamburger's method* (58).—A certain number of éprouvettes (eleven to sixteen) are filled with 10 to 20 c.cm. of saline solutions of different strengths. (These solutions differ by ·02 per cent.; thus the lowest is ·3 to ·4 per cent., whilst the second contains ·02 per cent. more, that is ·32 to ·42 per cent., the third ·34 to ·44 per cent., and so on.) ·5 c.cm. of blood are dropped into each of these and the mixture well shaken. After twenty-four hours have elapsed we notice in which tube there is no longer any hæmoglobin dissolved. This gives the isotonic concentration of the particular salt as regards the particular blood-corpuscles used, and the lower this concentration the greater is the resistance of the corpuscles to water. As Hamburger and myself (59) have repeatedly shown, the value of isotonic concentration for different salts is not a variable factor, but bears a fixed relation to their molecular weight. There are, however, differences as regards the blood of different animals, and consequently we must use solutions of the same salt in order to get comparable results as regards different specimens of blood. I consider the latter method far better than that of Landois, for the fact that we are dealing with much greater quantities ensures much greater accuracy. In Landois' method the corpuscles which first come into contact with the water are in a relatively dilute solution before the whole fluid becomes uniform. The only advantage of Landois' method is that a very small quantity of blood is required; on the other hand, the requirement of an appreciable amount of blood prevents Hamburger's method from being extensively used in clinical practice. To obviate this defect in what my experience shows to be, if carefully carried out, a reliable method, I propose the following small modification: it is better to use small glass vessels, like the one in Hayem's hæmocytometer, instead of the usual éprouvettes. Place in each a small, well washed and dried glass bead and then 1 c.cm. of the different solutions. The finger of the patient should then be pinched and a drop of the blood allowed to fall into each vessel. The mixture must be shaken for a minute in order to defibrinate it. The vessels should then be allowed to stand, in order of concentration, for six hours, and read off as above. It is

impracticable to test the fluid with the spectroscope, as some red corpuscles may stick to the sides of the vessel and cause the appearance of the absorption bands of hæmoglobin in the spectrum.

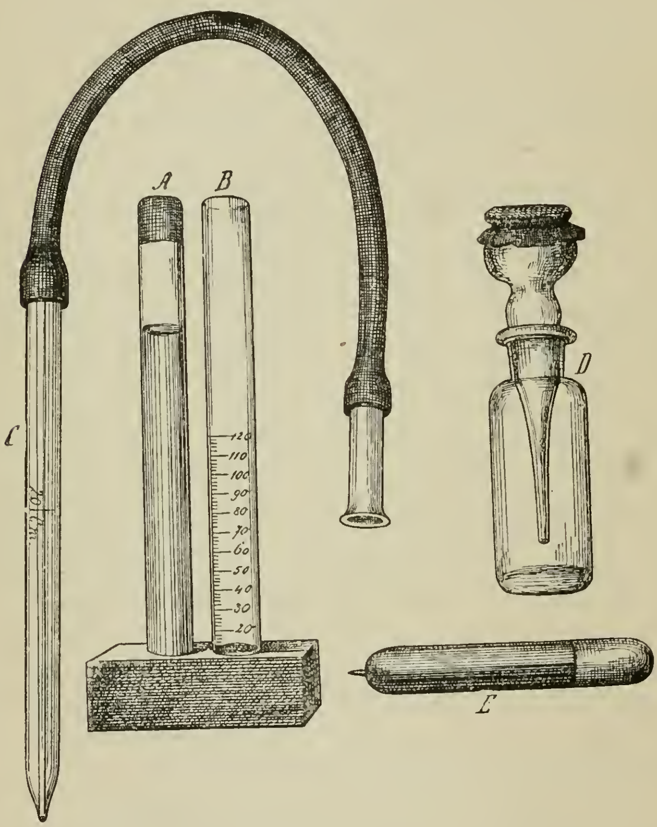
(3) *Laker's method* (60).—Laker measures the resistance of the red corpuscles to electric currents of high potential such as can be got from a Leyden's jar. This apparatus consists of the following parts :—A slide of hard rubber (10 cm. by 5 cm.) carries on its upper surface two isolated metal discs, between which are placed four similar capillary tubes (8 mm. long and 1 mm. diameter) in such a way that the current runs through all four at once. Opposite the metal ball connected with the inner coat of the Leyden jar is another connected with the outer coat, whilst the distance between the two balls can be regulated. Laker used a spark about 2 mm. long. Just before the beginning of the experiment the tubes are filled with blood freshly drawn from the body; the number of discharges which are necessary to lake the fluid are then noted. To test the blood of a patient fill one tube with his blood and the other three with normal blood. The difference in the number of discharges necessary gives a measure for the so-called specific resistance of the blood. In judging this method we must remark that it is not only the resistance of the red corpuscles that is measured, for other influences come in, especially uncontrollable variations in the conditions of the experiment, which are due to the unreliability of static discharges. In addition we are measuring an amount of resistance which never comes into play under physiological conditions, whilst the relatively complicated nature of the method will prevent its general adoption.

(4) *Maragliano's methods* (61).—In these the resistance of the corpuscles is investigated by observing at what point destruction begins under the influence of paraffin, heat, compression, drying, and different reagents. When we consider how comparatively crude these investigations are, and that we are in the dark as to what physiological properties are brought into question, it will be seen that these methods are not of great value.

(*d*) *Investigation of the hæmoglobin.*—A. Quantitative estimation of hæmoglobin.

1. *Gowers' hæmoglobinometer* (62) consists of two tubes of exactly equal calibre. Three quarters of one tube are filled with carmine-picrocarmine gelatine, the colour of which corresponds to that of a 1 per cent. aqueous solution of normal blood, and the tube is closed by a cork. The second tube has a scale of 10—120, and is the receptacle for the blood and the diluting fluid (distilled water). The apparatus consists also of a capillary pipette to measure off 20 c.cm. of blood (C), a drop-tube for the water (D), and a needle for

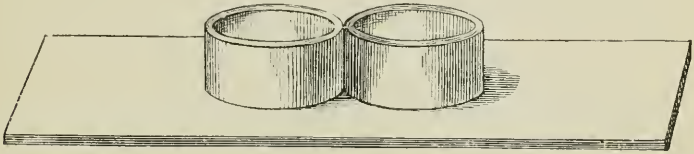
Fig. 9.



the extraction of blood (E). The process is as follows :—The finger is pricked, 20 c.mm. of blood are sucked up and blown out at once into the tube B, in which there are a few drops of water; the tube is shaken for about a minute to defibrinate the blood, and distilled water is dropped into it until the colour is the same as that of the tube A. For purposes of accurate comparison the tubes are placed in a wooden stand in front of a piece of white paper. The average of the heights of the upper and lower meniscus of the fluid gives the amount of hæmoglobin in percentages of the normal.

2. *Hayem's hæmoglobinometer* (63).—"Dosage d'hémoglobine." The apparatus consists of a double glass cell and a colour scale of picro-carmine, which is arranged in five circular layers.

FIG. 10.



The first consists of two glass rings, of exactly the same diameter, separated by a thin division, and fixed on a glass plate. The capacity of each is 500 c.mm. The scale is so arranged that the amount of hæmoglobin in—

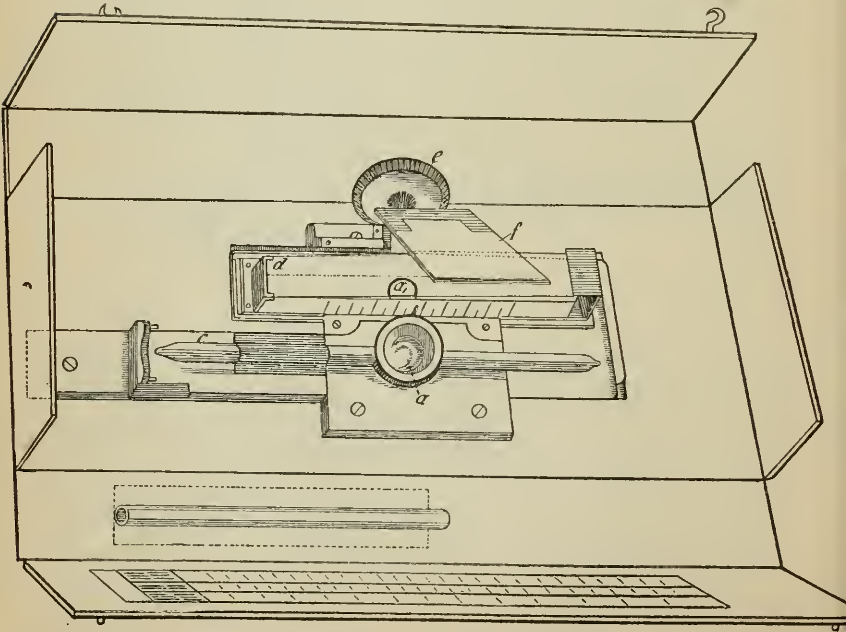
No. 1 corresponds with that of 8,866,000 normal red cells.
No. 2 ,, ,, ,, 9,973,000 ,, ,,
No. 3 ,, ,, ,, 11,081,000 ,, ,,
No. 4 ,, ,, ,, 12,189,000 ,, ,,
No. 5 ,, ,, ,, 13,297,000 ,, ,,

The estimation is made as follows :—500 c.mm. of distilled water are placed by means of a pipette in each cell. In one a few c.mm. of blood are dropped and well mixed with a glass rod (2—3 c.mm. of normal blood are sufficient, but in pathological cases the greater the deficiency of hæmoglobin the greater the amount necessary). The comparison is made by placing the scale under the other cell. We find the number of normal red blood-cells necessary to produce the same colour, and by counting the number of red cells in the specimen (which should be done at the same time) we have the relation of hæmoglobin to the normal. For example, in a specimen of blood the number of red cells is 2,580,000 per c.mm.; in estimating the hæmoglobin 7 c.mm. are used, and the colour is found to correspond to No. 3 of the scale. The hæmoglobin corresponds to that of 1,583,000 normal blood-cells. The estimation of the absolute amount of hæmoglobin and the relative deficiency presents no difficulty. The normal number of blood-cells being taken as 5,000,000, the relative proportion of hæmoglobin is $\frac{1,583,000}{5,000,000}$ —*i. e.* the percentage of the normal is 31·6.

Taking the normal weight of hæmoglobin as 14 per cent., the weight in this case is $14 \times \frac{1583}{5000}$ per cent. = 4·43 per cent.

3. *Mallassez' Hæmochrometer* (64).—The instrument consists of a screen in which are openings 2 to 5 mm. in width

FIG. 11.



(*aa*), capable of being closed by an obturator. The screen itself shuts in the rest of the apparatus, and can be put up in a small box. The bulb of a Potain-Mallassez mixer, which has plane walls 5 mm. from one another, is placed behind one opening (*a*). The long portion of the mixer rests in an elastic ring. Behind the second opening (*a*) is a glass prism (*d*) filled with picro-carminate of ammonia, which can be adjusted by a toothed wheel (*e*), and on which is a scale. A ground-glass plate (*f*), which can be placed over the openings, serves to disperse the light falling on it. The tables accompanying the apparatus give the values corresponding to the degrees and half-degrees on the scale. The mixer is filled with blood and distilled water in the proportion of 1 or 2 to 100, and then placed in the elastic ring. The whole apparatus is then held opposite a not too bright surface, and the prism is adjusted until the blood in the bulb shows the same colour as the prism.

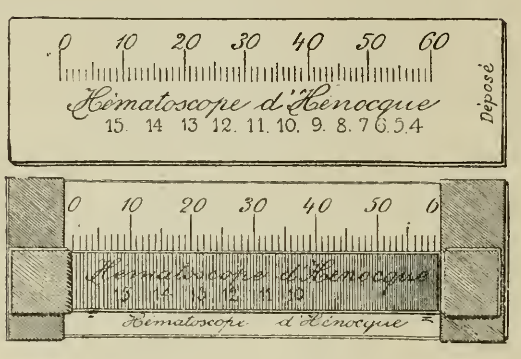
Table accompanying the Instrument.

Degree.		Absorption Capacity.		Amount of Hæmoglobin.
5	...	0·100	...	0·048
	...	0·110	...	0·053
6	...	0·120	...	0·058
	...	0·130	...	0·062
7	...	0·140	...	0·067
	...	0·150	...	0·072
8	...	0·160	...	0·077
	...	0·170	...	0·082
9	...	0·180	...	0·086
	...	0·190	...	0·091
10	...	0·200	...	0·096
	...	0·210	...	0·101
11	...	0·220	...	0·106
	...	0·230	...	0·110
12	...	0·240	...	0·115
	...	0·250	...	0·120
13	...	0·260	...	0·125
	...	0·270	...	0·130
14	...	0·280	...	0·134

4. *Hénocque's hæmatoscope* (65) consists of three parts: (i) An enamelled metal plate with a millimetre scale from

o to 60. Under this are placed the figures 15 to 4. The figure 15 is placed under the eighth mm. mark.

FIG. 12.



(ii) A glass plate of the same size, having the same mm. scale, with its end fixed in metal cases. The case over the 60 mm. end has a spur ·8 mm. in height. A second narrower plate can be fitted into the cases, resting above the larger plate, so that its under surface marks off a wedge-shaped space rising from the o mark to the 60 mark. Its thickness amounts to ·005 mm.

(iii) A spectroscope for direct vision after Browning. The apparatus can be used in two ways:

(*a*) The wedge-shaped space is filled with the blood by holding the widest part under the bleeding point of the finger. The retention of air bubbles must be carefully avoided. Plate 1 is now placed under Plate 2, so that the corresponding figures lie exactly over one another. The last of the figures (15—4) that is distinctly visible represents the amount of hæmoglobin in weight per cent.

(*b*) The second method is carried out as follows: The instrument is filled with blood as before. The glass is now held before the cleft of a spectroscope, and moved from o onwards until the characteristic bands of oxyhæmoglobin are distinctly seen. The values are then given by the following table, which goes with the apparatus:

13	millimetres	15·0	per cent.
14	,,	14·0	,,
15	,,	13·0	,,
16	,,	12·0	,,
17	,,	11·5	,,
18	,,	11·0	,,
19	,,	10·0	,,
20	,,	9·5	,,
21	,,	9·3	,,
22	,,	9·0	,,
23	,,	8·5	,,
24	,,	8·0	,,
26	,,	7·5	,,
28	,,	7·0	,,
30	,,	6·5	,,
32	,,	6·0	,,
35	,,	5·5	,,
39	,,	5·0	,,
44	,,	4·5	,,
49	,,	4·0	,,
54	,,	3·5	,,
60	,,	3·2	,,

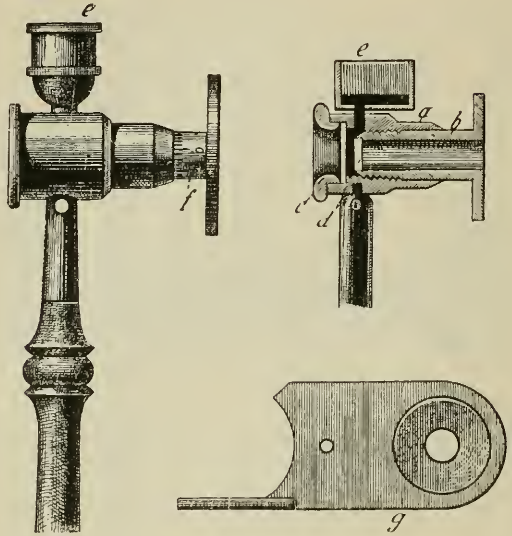
5. *Bizzozero's hæmo-chromo-cytometer* (66).—The principle of the instrument is:

(i) To find that thickness of a solution of blood of fixed strength which is sufficient to produce a certain depth of colour. In this case it is used as a "chromometer."

(ii) To find that thickness of blood in an isotonic saline solution, which prevents the eye from seeing a particular light. In this case it is used as a "cytometer."

The instrument consists of two tubes (*a*, *b*), each of which can be screwed into one another, and which are closed on the same side by a glass plate (*c*, *d*). On the upper surface of the outer tube is a small funnel-shaped vessel (*e*) which communicates with the tube by means of an opening. The space between *c* and *d* can be adjusted by screwing or unscrewing. If a fluid is poured in through the funnel, then on screwing up, the fluid will come out into the funnel. The inner tube has on its outer surface a scale (*f*) which gives the thickness of the layer of fluid. The screw is of such a pitch that one complete turn represents ½ mm. One division

FIG. 13.



of the scale represents ·02 mm. A red sample glass (*g*) is fixed in the instrument for use as a chromometer. In addition there are two éprouvettes with flat bottoms, a pipette holding ½—1 c.cm. and another holding 10—20 c.mm. When used as chromometer the disc (*g*) is fixed into it, 10 c.mm. of blood are measured off and mixed with ·5 c.cm. of water. The mixture is poured into the funnel, and the screw is adjusted until the colours correspond. When used as cytometer ·5 c.cm. of a 75 per cent. saline solution is measured off and mixed with 10 c.mm. of the blood. This blood-mixture is poured in through (*e*). The rest of the examination takes place in a dark room, in which a flame is placed about 1½ metres away from the instrument. The screw is adjusted until the upper three quarters of the flame are sharply marked off, and at this moment the scale is read.

It is assumed that in healthy blood the scale at this moment shows 110. The markings signify amounts of hæmoglobin as follows:

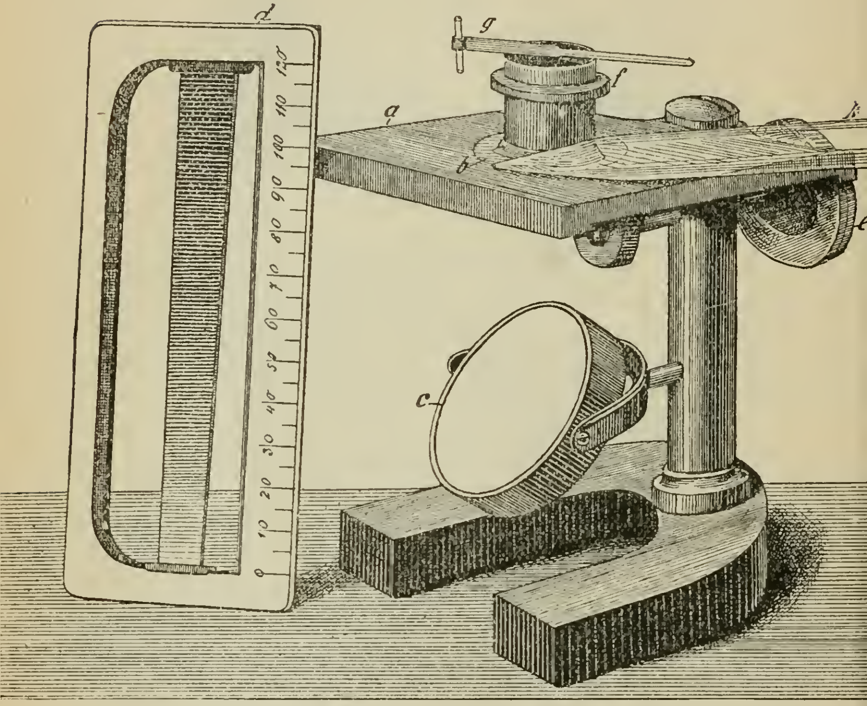
Cytometer degrees.	Hæmoglobin.
120	91·6
130	84·6
140	78·5
150	73·3
160	68·7
170	64·7
180	61·1
190	57·9
200	55·0
210	52·4
220	50·0

If on examination we find a specimen shows 110 cytometer degrees and 140 chromometer degrees, then these numbers represent the normal. We can thus easily get the values of the other chromometer degrees, but each instrument must be set as a chromometer before it is used.

6. *Fleischl's hæmometer* (67) consists of a small stand (*a*), like that of a microscope, with a circular gap (*b*) in its centre, under which a plaster plate is held after the manner of the microscope mirror. Under the stand a wedge-shaped red glass (*d*) coloured with Cassin's gold-purple can be moved up and down by a screw. A small metal vessel (*f*) divided into two halves by a diaphragm can be inserted into the circular hole. The bottom of this vessel is made of a circular plate of glass which can be screwed off. Some automatic capillary pipettes (*g*) in metal holders and a drop-pipette complete the apparatus, which can only be used by yellow light in a dark room. It is used as follows: The wedge (*d*) is fixed, and both divisions of the vessel (*f*) filled with distilled water. One of the automatic tubes is filled with blood directly from the finger. Every trace of blood must be removed from the outside of the tube, which is then inserted into one of the compartments (*f*) and shaken until every trace of colouring matter is washed out. The tube is now held perpendicularly over the vessel, and anything that remains, inside or outside, washed away by the drop-pipette (*h*). Both compartments are then filled up with water, care being taken that no meniscus is formed.

Finally the wedge is adjusted until the colours in the compartments correspond. A scale on the wedge represents the amount of hæmoglobin in percentages of the normal.

FIG. 14.



In the following tables Sadler and myself (68) have attempted to compare the values of the instruments of Gowers, Hénocque, Fleischl, and Bizzozero. These show at once, that Gowers' and Fleischl's are much preferable to the others. Their methods are, in the first place, very simple, and in the second freer from error. With regard to the Fleischl instruments I may remark that different instruments may give, as seen in the table, different absolute values. This is due to the colouring of the wedge, which cannot be exactly the same in all instruments. A little blue or yellow more or less (which are mixed with the red) must cause appreciable differences. Hence Delhio (69) recommends a correction-table to be made for each instrument before it is used clinically, by gradual dilution of a known solution of hæmoglobin. His own apparatus needed the following corrections:

	100	89·6	78·6	67·2	56·4	45·5	34·8	24·6	14·5
Correction ...	0	·4	1·4	2·8	3·6	4·5	5·2	5·4	5·5

Even these "correct" results depend upon there being no other source of error, such as may easily occur by inaccurate measurement of the capillary pipettes and the like.

TABLE 1.

Apparatus.	Gowers.	Hénocque.		v. Fleischl.	
		Direct reading	Spectroscope reading.	Old Instrument.	New instrument.
Red blood	107	14	14	112	118
9 cm.³ blood + 1 per cent. sodium chloride	87	14	11	95	112
8 ,, ,, +2 ,, ,,	83	14	9·3	88	103
7 ,, ,, +3 ,, ,,	73	13	8·5	75	87
6 ,, ,, +4 ,, ,,	62	13	7·5	68	74
5 ,, ,, +5 ,, ,,	58	12	6·5	65	58
4 ,, ,, +6 ,, ,,	50	10	5	58	49
3 ,, ,, +7 ,, ,,	40	7	4·5	40	34
2 ,, ,, +8 ,, ,,	26	6	3·5	28	25
1 ,, ,, +9 ,, ,,	10	<4	3·2	10	15

TABLE 2. (Sadler).

Degree; that is amount of hæmoglobin as shown by v. Fleischl's instrument.	Cytometer of Bizzozero.		Amount of hæmoglobin shown by the cytometer is greater than that shown by the hæmometer by	Chromometer of Bizzozero gives degrees.	Chromometer shows also amount greater or less than that shown by cytometer.
	Cytometer degree.	Amount of Hæmoglobin.			
110	95	115·7	5·7	102	+ 7
105	100	110	5	105	+ 5
100	105	104·7	4·7	108	+ 3
100	103	106·7	6·7	100	− 3
95	113	97·3	2·3	127	+14
95	110	100	5	114	+ 4
90	116	94·8	4·8	118	+ 2
85	120	91·6	6·6	114	− 6
80	130	84·6	4·6	143	+13
80	128	85·9	5·9	125	− 3

TABLE II (continued).

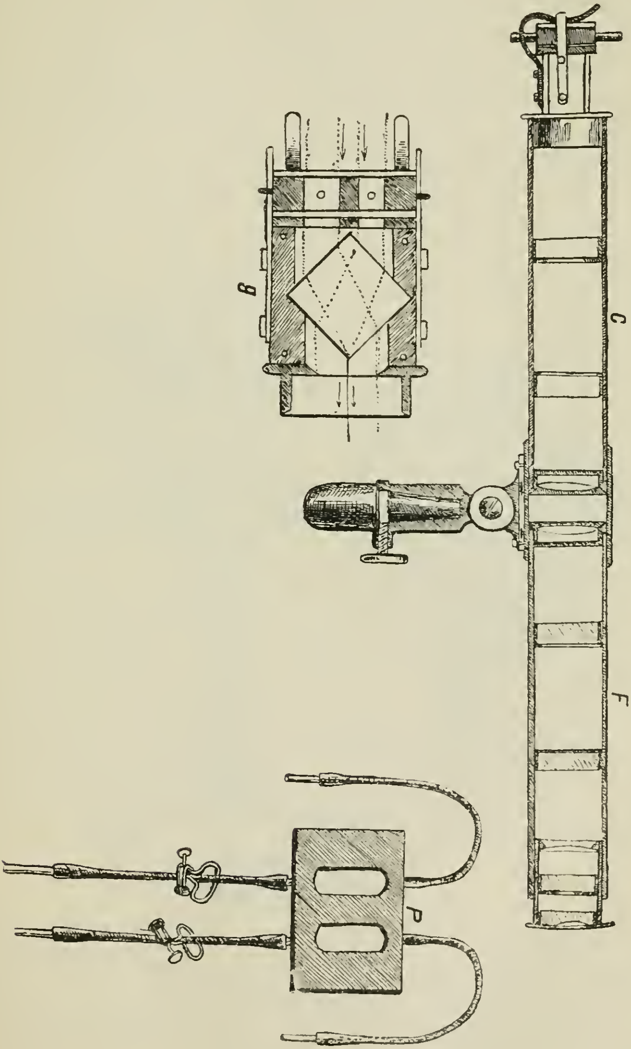
Degree; that is amount of hæmoglobin as shown by von v. Fleischl's instrument.	Cytometer of Bizzozero.		Amount of hæmoglobin shown by the cytometer is greater than that shown by the hæmometer by	Chromometer of Bizzozero gives degrees.	Chromometer shows also amount greater or less than that shown by cytometer.
	Cytometer degree.	Amount of hæmoglobin.			
80	127	86·6	6·6	117	−10
75	140	78·5	3·5	132	− 8
75	135	81·4	6·4	143	+ 8
70	147	74·8	4·8	150	+ 3
70	145	75·8	5·8	156	+11
70	143	76·9	6·9	140	− 3
60	167	65·8	5·8	155	−12
60	165	66·6	6·6	160	− 5
55	180	61·1	6·1	192	+12
35	276	39·8	4·8	266	−10

7. *F. Hoppe-Seyler's colorimetric double-pipette* (70).—This apparatus is now provided with an "Albrecht's glass cube" for a better comparison of the two fields of view. It consists of the following parts:

1. A telescope.
2. A collimator.
3. The special "double-pipette" of F. Hoppe-Seyler.

The telescope F and the collimator C are screwed into a straight tube resting on a cast-iron tripod, and revolving on a vertical and on a horizontal axis. A glass cube *g* is placed in the collimator-tube in a blackened case; this cube is grooved on four sides, so that two diagonally opposite corners lie in the optic axis of the telescope, and the angle nearest the telescope lies in the focus of the collimator lens. The apparatus is closed in front by a glass plate, and to this the special pipette is attached. This latter is formed by a rectangular brass plate (P), ·5 cm. thick, in which are cut two chambers separated by a bridge 3·5 mm. broad. If this brass plate is placed on the glass plate in front of the cube, and another glass plate superimposed and kept on by springs, two chambers are formed, each of which has two tubal openings. The light which now passes to the eye of the observer at the eye-piece of the telescope passes through both chambers, but is then so deviated by the cube, that they appear separated by a mathematical line. In this way the comparison is simplified.

FIG. 15.



There are also four thin rubber tubes and four glass tubes fitted on to the openings into the chambers, so that each has a fairly long tube, with a glass mouthpiece above, and a shorter tube with a longer glass mouthpiece below. The latter can be compressed by clips. In order to use this instrument we must have a so-called normal solution of hæmoglobin, the strength of which is known. This is prepared by Professor Hoppe-Seyler at the laboratory at Strassburg, and can be obtained from the attendant there in small sealed tubes containing 2·51 gr. of CO-hæmoglobin (dried at 120° C.) in 100 volumes of fluid. Five c.cm. of this solution are diluted with 50 c.cm. of water, and sucked up into one of the chambers from a small beaker. A small quantity of the blood to be examined is now measured off or weighed out, and carbon monoxide gas is carefully passed through, so that the hæmoglobin is converted into CO-hæmoglobin. Now a known amount of water shaken up with carbon monoxide gas is added from a burette, divided into $\frac{1}{10}$ c.cm., until the solution seems distinctly redder than the normal solution. The fluid is then sucked up into the second chamber, the difference of colour noted, and again let out by loosening the clip on the lower tube. The observer carefully adds carbon monoxide water to the solution in the beaker, shaking all the time, and repeatedly sucking up, examining, and letting out again, until the colour is exactly the same as that of the normal solution. The exact amount of carbon monoxide water required for this purpose is now read off the burette. The calculation is exceptionally simple. Let p be the weight of blood drawn off, c the percentage amount of hæmoglobin in the diluted normal hæmoglobin solution, v the volume of the whole solution when the colours correspond, and H the required percentage of hæmoglobin; then

$$H = \frac{v.\ c.}{p.}$$

If the solution becomes cloudy, a drop of dilute caustic potash will clear it up. The advantages of this instrument over the others are:

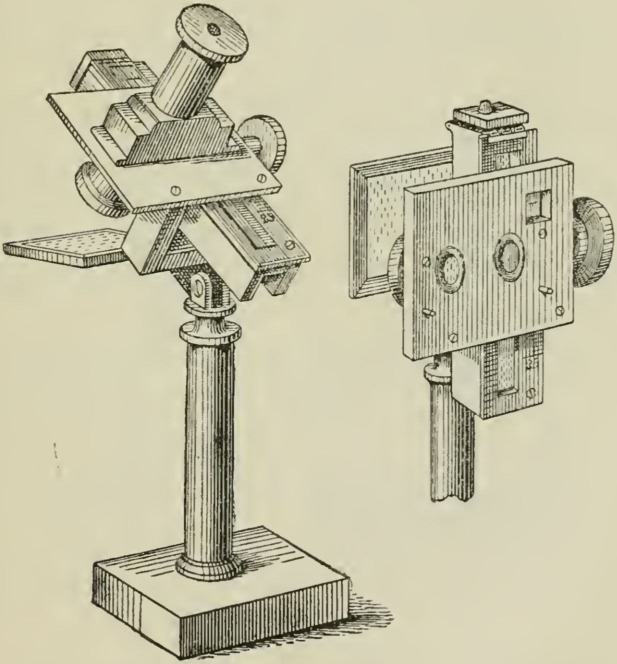
(1) That here hæmoglobin is compared with hæmoglobin, and not with coloured glasses or fluids.

(2) The use of the Albrecht cube, causing the most delicate differences of colour to be easily observed. This, on

the other hand, makes the method a very slow one compared with that of Gowers or Fleischl, and consequently the apparatus, though it is the most accurate, in my opinion, yet invented, and has been a long time before the public, has hitherto been but little used in clinical practice. Another disadvantage is that the normal solution must be freshly prepared—a long and wearisome process—or obtained from strangers.

(8) *Mallassez' new Hæmochromometer* (71).—(*Hémochromomètre à étalon fixe.*) This consists of a metal plate with two openings; behind one of these is a colour scale, and behind the other a glass prism for holding the blood solution. The colour scale is formed by a prism containing a picro-carmine solution representing a 5 per cent. solution of hæmoglobin. The vessel for the blood solution has the form of a long wedge with its base upwards, the base being

Fig. 16.



open. The sides are made of metal, and are joined by screws; they fix the front and back walls, which are made of mirror-glass. The vessel is fixed on to a piece of mechanism, and can be moved up and down. A third opening in the metal plate shows the colorimetric value. Beneath the apparatus is a small mirror which provides reflected light; the instrument can, however, be used by diffused daylight. There is, in addition, a small apparatus that can be placed over the two small central openings. This consists of two doubly-refracting prisms, a very narrow diaphragm and a microscope; two fields are thus brought side by side and magnified. The whole is placed on a stand, and by means of a joint can be used in the perpendicular or oblique position, according as we use reflected or direct light. There is also a mixer graduated to 100, its capillary portion being graduated to 1 and 2; a provisional mixing vessel and a needle. The blood is mixed with distilled water in the mixer in fixed proportion, transferred to the vessel, and the screw turned until both colours coincide. If the dilution is 1 : 100, the percentage of hæmoglobin, is given by the number seen in the opening. If the dilution is 1 : 200, this number must, of course, be multiplied by two.

For accurate estimations of the hæmoglobin in blood we must make either chemical or spectro-photometric examinations.

To find the amount of hæmoglobin in a specimen of blood by weighing, we estimate the amount of oxide of iron in the residue, and multiply by 166·7.

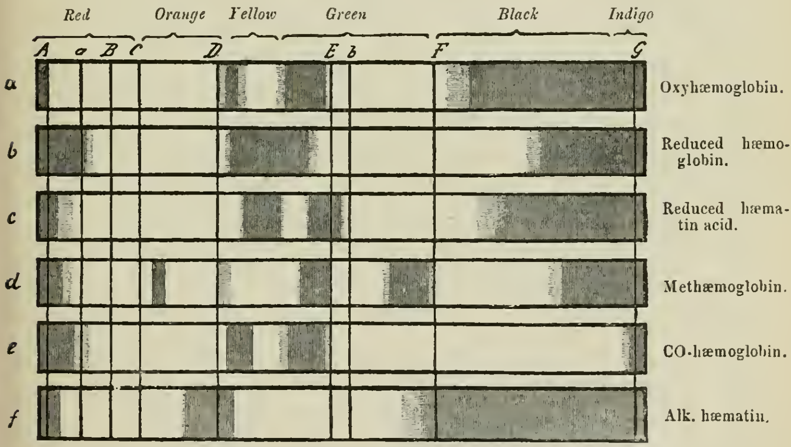
With regard to the spectro-photometric estimations, we must refer to the papers of Vierordt, Elan, Otto (spectrophotometer of Hüfner) and G. and H. Krüss.

B. Qualitative examination of hæmoglobin.—This examination depends upon the chemical behaviour of the hæmoglobin.

(*a*) *Qualitative changes in the hæmoglobin.*—We must use a spectroscope in order to show these. For clinical purposes one of the ordinary spectroscopes [*e. g.* the one with Hénocque's apparatus or Hering-Maschek's spectroscopes without lenses (72)] is sufficient. In using these we first look at ordinary daylight or lamplight and focus the Fraunhofer's lines as clearly as possible, and then place a vessel with plane parallel walls, containing the fluid, between the light and the chink. On examining the blood in which the hæmoglobin has undergone no qualitative change, we dilute sufficiently (about ½ per cent.) with distilled water; we then perceive two absorption-bands in the spectrum—the bands of oxyhæmoglobin (*a*) [Hoppe-Seyler (73)], which lie between the Fraunhofer lines *D* and *E*. The one near the red is narrower and more sharply defined than the one near the green.

If we now add a reducing substance *e. g.* ammonium sulphide, or if we reduce the pressure by means of an air-pump, the colour and the spectroscopic effects both alter. The fluid becomes bluish-red, and instead of two bands between *D* and *E* we have only one, namely, the spectrum of reduced hæmoglobin (*b*). On addition of acids or carbon dioxide gas, or strong alkalies, this can be changed into hæmatin, the acid solution of which gives the same spectrum as methæmoglobin in an acid solution (see below). In an alkaline solution hæmatin shows a somewhat narrower and less defined absorption-band than reduced hæmoglobin—*f* between *D* and *E*.

FIG. 17.



Clinically speaking the most important alteration of hæmoglobin is the change into methæmoglobin. With the naked eye we can see that the normal red has become a dirty chocolate brown. The spectrum of this body shows four absorption-bands (*d*) in acid or neutral solutions (Jäderholm) (74), the most distinct being between *C* and *D*. Two others lie between *D* and *E*, one close under *D* in the yellow, and one close under *E* in the green, whilst the fourth lies between *b* and *F*, nearer *F*, in the bluish-green. Dittrich (75), who has lately examined the spectrum of pure methæmoglobin, found only two bands, the one between *C* and *D* and the other at *D*. This spectrum is similar to that of acid hæmatin, but differs from it in that on addition of ammonium sulphide—this can only be seen on careful observation—it merges first into the spectrum of oxyhæmoglobin (*a*), and directly after into that of reduced hæmoglobin (*b*). Acid hæmatin, on the addition of ammonium sulphide, shows the spectrum of reduced hæmatin (*c*).

The change of normal oxyhæmoglobin into CO-hæmoglobin by the addition of carbon monoxide is also of great clinical importance. The colour of the blood becomes carmine-red and bluer than normal blood, arterial and venous blood being in this case alike. The spectrum (*e*) shows that the normal bands are displaced slightly to the right. Many tests for this change have been proposed, of which the simplest depends on the fact that on addition of ammonium sulphide the spectrum of oxyhæmoglobin becomes that of reduced hæmoglobin, whilst that of CO-hæmoglobin does not alter (Hoppe-Seyler). When both these substances are present this test fails, and therefore additional tests have been proposed. Hoppe-Seyler dilutes the blood-solution with 10 per cent. caustic soda, and warms it. Oxyhæmoglobin becomes a dirty brownish-green, whilst CO-hæmoglobin remains vermilion. Kuniyosi Katayama (76) adds ammonium sulphide and dilute acetic acid, and finds that CO-hæmoglobin remains unaltered in colour, whilst oxyhæmoglobin becomes grey-green. On heating neutral aqueous solutions of CO-hæmoglobin to the boiling point a light red coagulum is formed, whilst in the case of oxyhæmoglobin the coagulum is a grey brown. CO-hæmoglobin gives, on the addition of strong caustic soda, a light red precipitate, which on exposure to air slowly becomes brown, owing to formation of hæmatin (Hoppe-Seyler (77)). Dresser (78) has proposed a spectro-photometric method for the quantitative estimation of the CO-hæmoglobin and O-hæmoglobin.

(*b*) *Estimation of the resistance of hæmoglobin to chemical influence.*—Körber (79) proposed a method which was afterwards perfected by Krüger (80). These observers add 10 per cent. caustic soda or acetic acid to diluted blood-solutions of the same colour, or to solutions of oxyhæmoglobin of equal concentration, and find the point at which the characteristic absorption-bands disappear. They have found considerable differences in the resistance of the hæmoglobin in various diseases in man and in a large number of different animals.

IV. ESTIMATION OF THE DENSITY OF BLOOD AND OF PLASMA.—The density of the blood can be measured in a multitude of ways with varying accuracy. If we have a sufficient quantity of blood, then, undoubtedly the pyknometric (direct-weighing) method is the most certain; the araëometric method is quicker but less accurate. These two methods are the best for physiological purposes.

For clinical purposes, many methods have been proposed which require very little blood. Most of these are indirect—*i. e.* we endeavour to get a mixture of the same density as the blood or plasma by adding a fluid of heavier density to one of lighter density.

Schmaltz' (81) *method*—the capillary pyknometer—is a direct one, and the best, although it is the most complicated. A thin-walled glass tube is drawn out so that we have a capillary tube of about 12 cm. long, about $\frac{2}{3}$ mm. diameter at the open end, and about $1\frac{1}{2}$ mm. in the middle. This is carefully cleaned, dried, and weighed; then filled with distilled water and weighed again. The water is then blown out and the tube dried with ether and alcohol. The tube is now filled with blood by suction and weighed again. The specific weight of the blood equals the weight of the blood in the tube divided by that of the distilled water. This method is tedious and takes time, but it is the best method of dealing with a small quantity of blood as, in the hands of practised observers there are hardly any possible sources of error, save those which occur when the blood is obtained.

The following are the indirect methods of estimating the density of blood.

(1) *Fano's method* (82).—A drop of blood is allowed to fall into a solution of gum arabic of medium concentration, placed in an éprouvette ; if this sinks a stronger solution is added until the drop neither sinks nor rises. The specific gravity is that of the fluid and is at once found by inserting an araëometer.

(2) *Roy's method* (83) rests on the same principle—the fluid used being glycerine diluted with water. v. Jaksch (84) recommends that different glycerine mixtures of specific gravity 1035 to 1068 be kept ready in éprouvettes. A drop is allowed to fall into each glass, and the density of that one in which the blood neither rises nor falls is the density required.

(3) Hammerschlag (85) uses the same principle, but his fluid is a mixture of chloroform and benzol.

(4) *Haycraft's method* (86).—Two mixtures of benzoil-chloride (specific weight 1100) and toluol (specific weight ·8706) are prepared. The specific weight of the first mixture is 1070, and of the second 1020. These are placed in two burettes. A drop of blood is placed in a glass tube closed at one end, and the fluid poured into it from the two burettes until the drop just floats. The specific weight of the mixture is easily calculated. The mixtures should be prepared at 15° to 16° C. If the temperature is different at the time of observation, then for every 2° F. a correction, approximately ·88, must be made in the specific weight.

All these indirect methods are obviously adapted for rapid work, if the prepared solutions of known specific weight are kept in closed vessels.

Siegl (87) has made a scale of such mixtures in using the Hammerschlag method. As the fluids are very volatile, they must continually be tested and corrected. With regard to the reliability of the indirect methods we must remark that they all give higher values for the specific weight than the direct method. The Hammerschlag method is the best of the indirect methods, but here occasionally one part of the drop will rise and the other sink.

All these methods can, of course, be used to estimate the density of the plasma or serum. In the case of the plasma Hammerschlag recommends that the blood should be taken up in a capillary tube about $\frac{3}{4}$ cm. long ; this is previously plunged into a 3 per cent. solution of potassium or sodium oxalate, and the contents are then blown out. Both ends are closed with wax, and the tube allowed to stand for some hours in a perpendicular position. The tube is then filed at the junction of corpuscles and plasma, the wax removed, and the plasma blown out into the benzol-chloroform mixture, when the process is the same as with the blood. In estimating the specific weight of the serum, the blood is allowed to coagulate in a capillary tube. The method is then the same as in the case of the plasma.

V. ESTIMATION OF THE ALKALINITY OF THE BLOOD AND SERUM.—For the *qualitative examination* of the reaction of a specimen of blood the following methods are proposed :

(1) *Kühne's method* (88).—The blood is submitted to dialysis. For this purpose a so-called "spoon-dialysator" is prepared out of soaked parchment paper, and a small piece of this paper is made into the shape of half a sphere by the pressure of a small lead ball. The drop of blood is placed in this, and the whole floated in a watch-glass full of water. After a time the reaction of the water is tested with litmus.

(2) *Liebreich's method* (89).—The drop of blood is placed on a plaster or clay plate previously soaked in neutral litmus solution. When the plasma has been absorbed, the blood is washed off by a strong current of water.

(3) *Zuntz's method* (90).—Zuntz uses glazed litmus paper soaked in a solution of sodium chloride or sodium sulphate. A strip of this is wetted with the blood, and the latter immediately washed away by a jet of water.

Quantitative methods.

(1) *Zuntz's method* (91).—He uses diluted phosphoric acid, of which 1 c.cm. corresponds to ·005 gr. sodium carbonate, and neutral litmus, and estimates titrametrically.

Lassar (92) instead of phosphoric acid uses tartaric acid, 7·5 gr. to the litre, the reaction being more distinct.

(2) *Landois' method* (93).—This requires a Lassar solution of tartaric acid, a saturated neutral solution of sodium sulphate, and the finest litmus paper as an indicator. We prepare ten mixtures from the two solutions.

Mixture 1—10 parts tartaric solution—100 parts sodium sulphate solution.
,, 2—20 parts tartaric solution—90 parts sodium sulphate solution.
,, 10—100 parts tartaric solution—10 parts sodium sulphate solution.

A small glass tube about 1 mm. in width, which is finely drawn out, is filled with about 8 mm. of water, and the upper end of the column of fluid marked. The fluid is then drawn up so that its lower end corresponds with the mark when its upper end is again marked. In this way we can measure exact amounts of different fluids. Mixture 1 is drawn up to the lower mark, and then (after carefully cleaning the end) fresh blood is drawn from the finger up to the upper mark. The whole is now blown into a watch-glass, and the reaction tested. If it is still alkaline we repeat the process with mixture 2, and so on until we get an acid reaction.

The different mixtures represent the following amounts of alkali:

Mixture	1	.	·036 per cent. sodium hydrate.
,,	2	.	·072 ,, ,,
,,	3	.	·108 ,, ,,
,,	4	.	·144 ,, ,,
,,	5	.	·180 ,, ,,
,,	6	.	·216 ,, ,,
,,	7	.	·252 ,, ,,
,,	8	.	·288 ,, ,,
,,	9	.	·324 ,, ,,
,,	10	.	·360 ,, ,,

v. Jaksch (94) has modified this method. Like Landois he prepares two salt solutions, a $\frac{1}{10}$ normal tartaric acid (7·5

—1000), and a concentrated sodium-sulphate solution. The first solution is diluted ten and one hundred times (so that we have solutions of 1 in 100 and 1 in 1000 of normal solution), and eighteen mixtures made as follows :

Mixture 1. ·9 c.cm. $\frac{1}{100}$ normal acid and ·1 c.cm. sodium sulphate.
,, 2. ·8 c.cm. $\frac{1}{100}$ normal acid and ·2 c.cm. sodium sulphate.
,, 9. ·1 c.cm. $\frac{1}{100}$ normal acid and ·9 c.cm. sodium sulphate.
,, 10. ·9 c.cm. $\frac{1}{1000}$ normal acid and ·1 c.cm. sodium sulphate.
,, 11. ·8 c.cm. $\frac{1}{1000}$ normal acid and ·2 c.cm. sodium sulphate, and so on

One cubic centimetre of each mixture is placed in eighteen watch-glasses. Blood is withdrawn by cupping, and 1 c.cm. is dropped into each glass before coagulation has occurred. Each is at once mixed and tested with sensitive litmus paper. The different mixtures represent the following amounts of alkali.

Mixture 1 .	·360	sodium hydrate	in 100 gr. blood.
,, 2 .	·320	,,	,,
,, 3 .	·280	,,	,,
,, 9 .	·040	,,	,,
,, 10 .	·036	,,	,,
,, 18 .	·004	,,	,,

The method of Landois and its modification by v. Jaksch are not free from errors ; for instance, the solutions are not inert towards the blood, but cause the corpuscles to break up, and impair the accuracy of the computation. Again, as Kraus (95) has shown, only a portion of the salts are affected when a pigment is used. If litmus is chosen, we cannot get it exactly neutral, and none of the three alkali salts that can be formed from the three basic phosphates are neutral towards these colouring matters. Further, in adding an acid to a solution of sodium carbonate we cannot exactly fix the point of saturation, whilst the free carbonic acid given off, unless it is driven off by heat, will cause a change of colour in the litmus.

Winternitz (96) dissolves tartaric acid in a solution of sodium sulphate, so that the concentration of the first solution is $\frac{1}{10}$ of the normal, and that of the latter 10 per cent. He fills watch-glasses with the same quantity of blood, and an increasing quantity of the mixture, and tests with fine litmus paper.

Kraus (97) defibrinates the blood to be examined, adds ten times the volume of a 1 per cent. solution of sodium chloride, and allows it to settle in a conical glass. The clear diluted serum is removed, after some hours, by a capillary tube, and titrated with $\frac{1}{10}$ normal hydrochloric acid, litmus being used as an indicator.

Tauszk (98) has altered the last process. In a graduated glass, constructed for this purpose, he measures off 10 c.cm. of ·6 per cent. solution of sodium chloride, and mixes it with a few drops of tropæolin or litmus solution. The glass has a pipette with a rubber tube. The whole is accurately weighed. Blood is taken from the finger, sucked up by the pipette, and dropped into the solution. The whole is now weighed again, so that the weight of the blood is known. The serum is now titrated with $\frac{1}{100}$ normal sulphuric acid.

All these methods estimate not the alkalinity of the blood, but that of the plasma or serum. The salt solutions prevent the red corpuscles from being dissolved. As the red corpuscles certainly contain acid-holding substances, and the amount of serum in the blood is not constant, these methods merely give the alkalinity of an uncertain amount of serum contained in the blood.

One of the errors is eliminated by *Löwy* (99). He titrates laked blood. The solution of the red corpuscles is made by the addition of ·2 per cent. solution of ammonium oxalate, in order to make their alkali accessible. To prevent the coagulation of the blood Löwy places 45 c.c. of the oxalate solution in a vessel, holding 50 c.cm., and lets blood run in up to the mark. The weight of the blood is exactly measured by $\frac{1}{10}$ cm. marks, just above and below the chief mark. After mixture the alkalinity is estimated by $\frac{1}{25}$ normal solution of tartaric acid and litmus paper. This latter is made by steeping paper in an alcoholic solution of litmus, neutralised until violet coloured by hydrochloric acid. A drop of the blood-mixture is placed on the dried paper; circular zones are then formed by diffusion, and distinctly show the reaction. This process is independent of the temperature and of the time taken. The alkalinity obtained by this method is much higher than that obtained by those previously mentioned.

C. Schultz-Schultzenstein (100) gives a clinical method in which only a minute amount of blood is required, and the red corpuscles are dissolved, so that we obtain the total alkalinity.

A drop of blood (7·5 mg.) is drawn up in a capillary tube like the one with Fleischl's hæmometer, diluted with neutral water to 12 c.c., and over-acidified with 1·5 c.c. of $\frac{1}{100}$ normal sulphuric acid. This is well mixed; after mixing, a solution of erythrosin (iodosin) in ether is added, and the whole titrated with $\frac{1}{600}$ normal caustic potash, continually shaking until the ether layer shows the first appearance of red. The titration must be done quickly, otherwise an erythrosin-coloured flake of fibrin is formed between the fluids, and spoils the experiment.

These two last methods give the alkalinity, not of the plasma, but of the whole blood. Now the acid-binding powers of blood and serum are caused by two groups of substances, apparently biologically different, viz. the acid salts and the albuminoids. It is questionable whether the latter are of as much account biologically as acid substances. Hence, the chief effect of an alkalimetric method should be to determine the amount of alkali due to the acid-holding salts. It also seems advisable to use either pure blood or pure serum. With this view I (101) have worked out a method for estimating the alkalinity of blood and of serum, which rests on the known relations of the albuminoids towards free acids.

Drouin (102) has proposed a method which is adapted for clinical purposes. In this ·5 c.c. of serum are heated with 1 c.cm. of water, and one drop of an alcoholic solution of phenol-phthalein added; the mixture is then titrated with $\frac{1}{1000}$ normal sulphuric acid.

VI. Measurement of acidity.—Maly has called attention to the fact that blood and serum contain many chemically unsaturated combinations, and from a certain point of view should be considered as acid; for instance, blood-serum has an acid reaction with regard to phenol-phthalein. The amount of acid reaction, or power to combine with bases, is given by the sum of the salts that still have the power of combining with bases (*i. e.* apart from the organic acid salts), more especially acid phosphate ($NaH_2 PO_4$). Whether the neutral phosphate ($Na_2H PO_4$), in spite of its holding an unsaturated atom of hydrogen, can combine with bases is not certain. The fact that Kraus found relatively high values, seems to show that neutral phosphates must, in his method, be regarded as being able to combine with basic compounds.

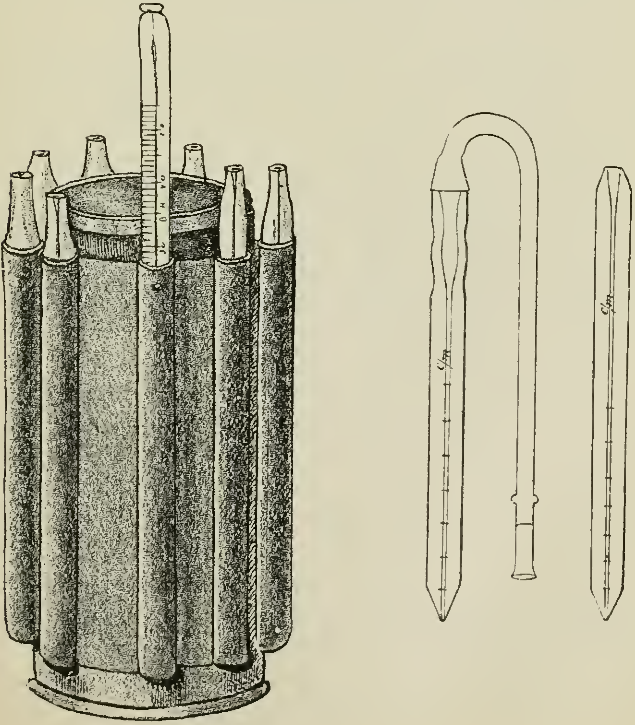
Kraus's method (*loc. cit.*).—Blood is allowed to flow from a vein (or the carotid) of an animal into a vessel in which there are 5 c.c. of a saturated alcoholic solution of potassium acetate. This is prepared as follows: 1 volume of a saturated solution of potassium acetate is made with water, and then a quarter to three eighths of its volume of alcohol added. The vessel is weighed before and after the addition of the blood. The specific gravity of blood being taken as 1·05, we have the volume added. Potassium acetate in solution is now added until the blood is diluted in the ratio of 1 : 5. Twenty c.c. of a filtrate of the mixture are now taken, and a known amount of baryta solution added (about 3 c.c. of a $\frac{1}{10}$ normal baryta solution to 20 c.c. of fluid). The mixture is filtered, and the excess of baryta in an aliquot portion of the filtrate titrated with $\frac{1}{10}$ or $\frac{1}{1000}$ normal hydrochloric acid. The rest of the baryta (except a small portion taken up by the carbonic acid contained in the solution of potassium acetate, which must be allowed for) represents the basic capacity of the blood. During the experiment it is absolutely necessary to avoid the access of atmospheric air to the alkaline baryta solutions.

Drouin's method (*loc. cit.*).—Half a cubic millimetre of serum is mixed in a closed bottle with sufficient sodium hydrate to neutralise all acid affinities. Barium chloride is now added, so that all the carbonates, phosphates and urates, are precipitated. The mixture is filtered, and the alkalinity of an aliquot portion estimated. Drouin compared the values so found with the dry residue.

VII. Estimation of the time of coagulation of blood.—In spite of the obscurity of the nature of the coagulation of the blood, repeated attempts have been made, clinically, to measure the differences—apparently great—of coagulative power in different cases.

Vierordt's method (103).—Sufficient blood is taken from a prick in the finger to fill about ½ cm. of a glass capillary tube of 1 mm. diameter and 5 cm. long. A white horse-hair, cleaned with the greatest care, and about 10 mm. long, is placed in this, and slowly moved about, the tube being held still. At first small portions of blood stick to the hair, then, when the coagulation begins, small clots adhere to these, and as soon as the coagulation has ceased the hair becomes free. The time of this is noted, and the difference between it and the time of the extraction of blood is the time required.

Fig. 18.



Wright's method (104).—This apparatus (Fig. 18) consists of a leather case, and contains a metal vessel to hold lukewarm water. On its exterior are nine leather sheaths, one of which carries a thermometer, whilst the others contain capillary tubes. Blood is drawn into the tubes at fixed intervals, and after half to one minute an attempt is made to blow it out from the tubes; when we are unable to move the blood in the tubes in this way, it has become coagulated. The time required for coagulation is the difference of time between the filling of the tube and the ineffectual attempt to empty that tube in which coagulation has first occurred. During the estimation the temperature must remain constant 18·5° or 87° C.

Both these methods are full of errors. The latter has the advantage of being made at a constant temperature, but nevertheless does not seem to me to give sufficiently trustworthy results. Again Vierordt found the most striking differences in his own blood on the same day.

VIII. Measurement of the "Osmotic elasticity" of plasma and serum.—Most of the methods are purely chemical or bacteriological. For these I must refer my readers to the text-books on the subject, and will only mention those methods which serve to measure the so-called hypertonic value of the plasma and serum. These are the so-called plasmolytic method of de Vries (105), the corpuscular method of Hamburger (106) and the freezing-point method. By the first method we try to find that amount of water which is just sufficient (on addition to a fixed amount of the fluid to be investigated) to cause plasmolysis, *i. e.* dissolution in plants or blood-cells. We may use the epidermic cells of *Tradescantia discolor*, *Curcuma rubricaulis*, or *Begonia manicata* (Hamburger). This method, especially in the case of animal fluids, has no advantage over the much simpler method of Hamburger. Fixed amounts of the fluid (serum, ascitic fluid, etc.) are mixed with fixed quantities of water in increasing proportions. A drop of blood is placed on the mixture in each flask. The isotonic concentration of the blood is estimated at the same time. The row of flasks is allowed to stand for twelve hours. In the first set the corpuscles have then settled to the bottom, and the serum above is free from hæmoglobin. Towards the end the serum becomes more and more deeply coloured. The concentration of the fluid is noted in that glass in which the colouring of the serum is first seen. The isotonic value of the corpuscle being known, the hypertonic value of the serum to be examined, or the osmotic elasticity, is easily calculated. For example, if an addition of 4·8 c.c. of water to 5 c.c. of serum just fails to dissolve blood-corpuscles with an isotonic value of ·46 per cent. of sodium chloride, then the amount required $= \frac{(5 + 4{\cdot}8)\ 0{\cdot}46}{5} =$ ·901 per cent. sodium chloride.

This method is not only very simple but very accurate, for Hamburger (107) has shown that a difference of ·005 per cent. can be detected by means of it. It, therefore, excels the previous method, and has only two drawbacks; first, that a considerable quantity of serum is required, and, secondly, that ten to twelve hours are necessary for the experiment. In these two respects the freezing method has an advantage (Ostwald (108)).

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CHAPTER II.

THE QUANTITY OF BLOOD.

If we consider the close relations existing between the blood and the tissues, it is obvious that the quantity of blood must be greatly influenced by the changes, physical and pathological, which the body undergoes.

It is improbable, however, in view of the intimate relations between the blood, the lymph, and the tissues, that the variations in quantity—at any rate under normal conditions—are of any considerable degree. There is no method yet invented by which we can estimate the amount of blood of an individual in a simple manner, without danger to life or health. We have consequently very few data regarding the physical and pathological variations of the amount of blood in man, and we are obliged to make inferences from the concentration of blood of the diminution or increase in amount. We judge this concentration by counting the corpuscles, or by estimating the density of the blood. These methods can have no value apart from the fact that they show those variations which hold for a short space of time; they cannot speak with accuracy for the whole blood, as the observations are based, as a rule, upon an examination of blood taken from the superficial vessels of the skin. Further, the possibility of an increased formation or destruction of blood enormously increases the uncertainty of our inferences. According to Vierordt the average amount of blood in man is about one thirteenth of the body-weight.

With regard to the *increase of blood*. Under physical conditions, taking into account the regulatory functions of the tissues, and especially of the kidneys, we may say that only a small increase can occur, and that for a very short time. An increase should occur when fluid is added to the blood; this fluid, however, is rapidly excreted by the kidneys, as Forbes (1) showed by experiments upon himself. Thus at 6 a.m. he drank 600 c.c. of water; at 12 noon he passed 513 c.c. of urine.

On drinking 900 c.c. of water he passed 826 c.c. of urine.
„ 1500 „ „ 1186 „
„ 1800 „ „ 1433 „

Similarly a relative *diminution of blood* under physiological conditions can only be a slight one and of short duration. After profuse perspiration or copious watery evacuations we get diminution of the amount of blood with increased density. Tarchanoff (2) has used computations of the number of corpuscles in these cases to estimate the quantity of blood. This method is not satisfactory, for apart from other difficulties, no counting apparatus is sufficiently accurate to account for small differences.

Pathological variations in the amount of blood played a great part at the time of the humoral theory of medicine, but neither its extent nor its origin were at all clear. Plethora, or the relative increase of the mass of blood in the body, which, in later authors (*e.g.* Andral (3) and Piorry (4)) has been confused with polycythæmia, was of especial interest. Several forms of *plethora* were distinguished (5):

(1) *Plethora vera* (*Plethora ad molem, Plethora sanguinea*), *e.g.* polyæmia, a condition in which the blood was said to be increased in amount but unaltered in quality by luxurious living. This at the present day is called "full-bloodedness," and is characterised by a strikingly ruddy countenance, injection of the mucous membranes, powerful action of the heart, full and tense pulse, attacks of palpitation and dyspepsia, together with a feeling of suffocation. In post-mortems on such cases the organs, especially the heart, are said to be engorged with blood.

(2) *Plethora apocoptica* (*Plethora ad vasa, Plethora ad spatium*).—It was held that there was no increase of the blood in general, but that blood was driven out of one portion of the body and so caused plethora in the rest. The

condition which was supposed to arise in the rest of the body when an Esmarch's bandage was applied to a limb is an example of this.

(3) *Plethora serosa* (*Plethora hydræmia*).—Increase in volume of the blood, but relative dilution.

These three forms are recognised by some even now; certain others have only an historical interest.

The doctrine of plethora, formerly a dogma, has received its death-blow, owing to the growth of experimental investigation. It was especially due to the works of v. Lesser (6), Worm-Müller (7), and Cohnheim (8), that the possibility of the persistence of a condition of plethora came to be denied. Some observers, however (Oertel (9), v. Recklinghausen (10), Bollinger (11)), have lately, to some extent, returned to the old doctrines. v. Lesser and Worm-Müller tried to produce plethora artificially by transfusion into an animal, and came to the conclusion that this was possible, but only for a very short time. At first the vessels enlarge to receive the excess, and the pressure of blood is increased; but a portion of the injected blood quickly leaves the vessels, the lymph-stream increases, and the primary increase of blood gives place to an increase of blood-corpuscles, *i.e.* to a polycythæmia which gradually disappears. The animals never show any pathological symptoms, even when enormous quantities are injected. When 80 to 100 per cent., approximately, of the estimated amount of blood is added there are no pathological symptoms, and it is not until one and a half times the amount is injected that the animals succumb (Klikowicz (12) and Brasol (13)). Worm-Müller holds that half the injected fluid leaves the vessels within a few hours after a plethora vera has been produced in this way, while the cellular elements remain, and are consequently present in greater numbers—*e.g.* a rabbit was transfused for fifteen seconds from another rabbit, and the red corpuscles were counted:

Red corpuscles	before the experiment	5,160,000
„	after 2 minutes	5,870,000
„	„ 7 „	7,600,000
„	„ 14 „	7,580,000
„	„ 22 „	8,280,000

This polycythæmia does not last long. As a rule a few days suffice to restore the old relations—*e. g.* Worm-Müller found that the number of corpuscles were reduced to the normal in two days. In another experiment, in the case of a dog in which the quantity of the blood had been increased by 28 per cent., thirty minutes after an addition of 58 per cent. was made to the blood the red corpuscles had risen from 6·4 to 8·7 millions; but this increase had disappeared after twenty-three days, consequently both plethora vera and polycythæmia are transitory when produced artificially.

Cohnheim based his assertion that plethora could not exist chiefly on these experiments of Worm-Müller; but these experiments only showed that it was impossible to produce a condition of plethora artificially in the above way. The attempts to produce a plethora serosa in animals also failed. Repeated injections of isotonic salt solutions into the blood showed that, owing to the activity of the kidneys, a plethora serosa produced in this manner only lasts for a very short time.

Hamburger (14) has attempted to solve the problem of artificial plethora from a new point of view. He attempted to increase the power which blood, by reason of its salts, has of attracting water, by increasing the concentration of the salts. He injected large quantities (up to seven litres) of a relatively concentrated salt solution (5 per cent. sodium sulphate) into horses, and found that though more water passed into the serum for a time, yet it had begun to diminish within ten minutes; further, the serum had returned to its normal constitution, so that, on the injection of hypertonic solutions, the regulatory apparatus acts even more rapidly than in the other cases, and the normal relations of the blood are restored in a relatively shorter time. The observations of Oertel revived the old doctrine of plethora, in spite of the fact that old and new experiments showed that an artificial plethora vera or serosa could not be produced. According to him the fact that we can often remedy the lack of compensation in heart failure by limiting the amount of fluid taken up and methodically exercising the heart-muscle, suggested that the amount of blood was relatively increased at the time of this lack of compensation and that owing to the limitation of fluid the amount of blood was diminished and the work of the heart rendered easier. The clinical blood-investigations made in such cases by Lichtheim (15), Kisch (16), and Bamberger (17) could, of course, only specify qualitative changes, but they found no grounds for assuming that a plethora serosa existed in heart-failure; on the other hand, they found nothing to controvert Oertel's view, that quantitative changes might exist. In spite, however, of the fact that neither experimental nor clinical investigations could give any positive results as to the existence of plethora, Oertel's hypothesis was supported by the data collected by Bollinger and Bergmann (18) and by Heissler (19), for these showed not only that the relative quantity of blood and the relative size of the heart underwent the greatest variations in different animals, and also in men, but that the condition of nourishment of the body, especially the greater or smaller development of muscle and of fat, had an important influence on the relative quantity of blood, and on the relative weight of the heart. The following are some of Heissler's data (obtained by Panum's method):

Pigs	average	quantity	of blood	$\frac{1}{22}$	of	body-weight.
Cattle	,,	,,	,,	$\frac{1}{13}$	,,	,,
Sheep	,,	,,	,,	$\frac{1}{12}$	,,	,,
Dogs	,,	,,	,,	$\frac{1}{11}$	,,	,,
Horses	,,	,,	,,	$\frac{1}{10}$	,,	,,

The average relation of the weight of the heart to the body-weight is—

In pigs	1 : 220
In sheep	1 : 162
In horses	1 : 147
In hares	1 : 132
In deer	1 : 86

From these data it follows that the amount of blood and the weight of heart-muscle bear a direct relation to the muscular development, and an indirect relation to the amount of fat. In animals which are poor in fat and live a very active life, such as dogs, hares, and deer, the amount of blood and the weight of the heart are relatively great; whilst animals of indolent life and much fat, such as sheep and pigs, have a small heart and little blood.

Bollinger attempted to supply the link between these facts in animals and the assumption of a possible plethora in man by the observation that in man there are also great differences in the capacity of the blood-vessels; thus the aorta may vary in different persons by three times its width. All this makes it probable that in man the quantity of blood is subject to important variations; it does not, however, give a pathological significance to plethora, although we may expect acrobats and athletes to have an increased quantity of blood and a relatively large heart. Plethora in such cases is certainly not a pathological feature, for these people enjoy excellent health. Again, Bollinger finds dilatation and hypertrophy of the heart in the Munich beer-drinkers, and argues that the blood is increased in quantity, and so causes dilatation of the heart. We cannot accept this conclusion without further proof, for, as we have seen, plethora may exist without interfering in the least with the general health. According to Bollinger, however, a relative increase of blood can occur; but whether this is normal or abnormal need not be discussed. The estimations of the density of blood made lately have also tended to this conclusion: nevertheless a pathological signification of an increase in the quantity of blood has not yet been shown; on the contrary, all the observations seem to show that an increased volume of blood does not necessitate any injury to health.

Oligæmia, or inasmuch as the blood is more concentrated *anhydræmia,* is the converse of plethora.

Acute oligæmia is the result of rapid loss of blood, and produces death by lowering the blood-pressure. The rapidity and continuity of the bleeding is of the greatest importance; thus if the blood is lost so slowly that the regulatory apparatus has time to restore the loss of fluid, by withdrawing it from the tissues and lymph-channels, then the oligæmia, like plethora, is transitory, although it causes dilution of the blood, oligocythæmia, and usually hydræmia. If the loss of blood, however, is rapid and continuous, the blood-pressure sinks rapidly, and convulsions and death occur. In this case the cause of death is not due to the fact that the loss of corpuscles disturbs the functions of important organs, but depends directly upon the loss of volume, the actual oligæmia. The question of how great an immediate loss is consistent with life cannot be at once answered, for it depends, in the first place, on the rapidity of the bleeding; and in the second, the amount of reserve fluid in the body. Certain experiments which have been made (*e.g.* Vierordt's [20] showed that dogs and rabbits die when the blood-corpuscles have been reduced to 70—50 per cent. of the normal) are not sufficient proof. Panum's (21) observation is important, viz. that animals allowed to bleed to death retain about one third of their blood, so that an immediate bleeding of two thirds of the volume of blood should, as a rule, be at once fatal. It must be noticed, however, that even after a great loss (the individual being rich in fluid) the original volume of blood is apparently very rapidly restored, as is seen in the following experiment:

One litre of ·6 per cent. sodium chloride solution was poured into the stomach of a dog—weight 31 kg.—by means of a stomach-pump. The original number of corpuscles was 6,000,000. The animal was bled to 450 c.c., and the corpuscles, on being counted, became fewer and fewer, until, after forty-three minutes, a minimum of 5,220,000 was reached. The animal was again bled to 595 c.c. The minimum number of corpuscles was reached in thirty-five minutes, being 3,780,000. Let x be the volume of blood, a the amount of bleeding, b the number of corpuscles before bleeding, and c after. Then $x(b - c) = ab$. Hence the first volume of blood $= \frac{450 \times 6{\cdot}6}{6{\cdot}6 - 5{\cdot}2} = 2121{\cdot}4$, and the second $= \frac{595 \times 5{\cdot}2}{5{\cdot}2 - 3{\cdot}78} = 2178{\cdot}8$. These are approximately equal.

We do not know whether oligæmia without increased density can exist, but Stintzing and Gumprecht argued that it might occur in run-down individuals who had a normal number of corpuscles. This cannot be proved any more than its converse; but Czerny's experiments, showing that the blood, even when there is great poverty of fluid, still retains it proportional weight to the tissues, is against it.

Anhydræmia can be caused by excessive loss of fluid, *e.g.* in profuse perspiration or diarrhœa. That this loss is controlled by a regulatory apparatus is shown by the everyday experience that diminished ingestion of fluids will check profuse sweating. The pathological meaning of the concentration of blood caused by loss of fluid has been lately considered by Czerny (23), who came to the following conclusions :

"Increased density of blood, due to loss of fluid, leads by a slowly progressive central narcosis to death. This occurs not directly from the actual loss of fluid, but from the rapidity of its loss. It is the result neither of the diminished volume of the blood, and so an insufficient filling of the vessels ; nor of an increased viscosity and a consequent obstruction to circulation. As death is due to the mechanical results of the concentration of blood, its cause must be looked for outside the circulation. It is possible by subcutaneous injection of normal saline solution to prevent the appearance of the concentration ; it was consequently assumed that the want of water in the tissues caused a disturbance of the natural processes of diffusion ; but it was found that when fluorescin was subcutaneously injected (the rapidity of its diffusion being measured by its appearance in the urine), no difference occurred between the diffusion in normal cats and those which had been subjected to great losses of fluid. It appears probable, therefore, that death is due to some chemical substance which acts upon some central vital mechanism."

Anhydræmia as well as plethora seems thus to be deprived of pathological significance, but they are both of some clinical importance, for by their appearance or disappearance—*i. e.* by an increased or decreased density of the blood—we are able to observe the amount of interchange between the blood and the tissues.

Every addition or loss of fluid, even of small degree, must cause some, even if transitory, alteration in the volume of the blood. The same effect is obtained if fluid is interchanged between the vessels and tissues in response to a stimulation of the vaso-motor system, or the introduction of lymph-forming substances (Heidenhain [24]) ; for example, a dilatation or contraction of the peripheral vessels brought about by means of heat or cold. This was shown to be true as regards nervous influences by Cohnstein and Zuntz. On producing a dilatation of the vessels by cutting the spinal cord above the origin of the splanchnic nerves, they found a diminution of the number of red corpuscles in the blood. The actions of the above influences on the amount of the contents of the vessels have lately been studied by E. Grawitz (26) and Knöpfelmacher (27). These authors estimated the density of the blood and counted the number of corpuscles. A loss of density and diminution in the number of corpuscles indicates a relative increase of the volume of blood, and *vice versâ*. Grawitz found that perspiration appreciably increased the density of the blood. Leichtenstern (28) and Wick (29) made similar experiments, and showed that variations of density could be caused by different influences, injections, etc. If this is so, variations probably occur in different pathological conditions. The above may perhaps have some bearing on the profuse sweats of tuberculosis, pneumonia, and acute rheumatism.

We may summarise our knowledge of the physical and pathological variations in the volume of blood as follows:—The healthy body contains a regulatory mechanism by which an abnormal increase or decrease in the volume of the blood is checked. It has hitherto not been found possible to produce lasting plethora, and although some clinical and anatomical facts appear to indicate that the blood of animals and of men may have a relatively large volume, none of them give a pathological significance to such an increase. Oligæmia causes death by loss of blood, but an increased density of blood due to a moderate degree of oligæmia seems to be of no pathological significance. Variations in the volume of blood within narrow limits can be caused by many physiological and pathological influences, but these variations are soon neutralised by the fluids in the tissues.

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CHAPTER III.

THE CHEMICAL AND PHYSICAL PROPERTIES OF BLOOD.

C. Schmidt's (1) view, that the knowledge of the chemical constitution of the blood was of subordinate interest so long as it is not known in what proportion the particular components are divided between the blood and plasma or serum, still holds good. Formerly it was thought that the corpuscles were saturated with the constituent parts of the plasma (Prevost, Dumas); and Schmidt, taking yeast as an example, was the first to show that the *a priori* view, that living cells with penetrable walls must have the same composition as the medium in which they exist, is not founded on fact, and is not true so far as the blood is concerned. The same author has shown that there are certain physical relations between the contents of the corpuscles and the intercellular fluid; but so far our knowledge is not extensive enough to enable us to draw conclusions as to the constitution of the corpuscles simply from a knowledge of the constitution of the serum.

Hence an analysis of the whole blood does not give us the composition of the blood, nor is an analysis of single constituent parts sufficient. It is necessary to make, first, a complete analysis of the whole blood; and then a similar one for a constituent part, *e. g.* the serum. We might then estimate the distribution of different substances in the blood by means of a computation of the volumes of corpuscles, but the unreliability of our methods for estimating the volumes reduces the value of such an experiment.

The chemical composition of the blood is the product of the composition of the corpuscles of the plasma and the relative volume of each of these in the blood. The greater the proportion of any constituent to the whole blood, the nearer is its constitution to that of the latter. The constitution of the corpuscles was, until lately, thought to be fairly constant, but Hamburger (2) and Lehmann (3) have shown that the substances in solution in the corpuscles are undoubtedly subject to variations owing, amongst other things, to respiration. These variations were first accurately considered in certain investigations of my own, which were carried on in connection with a number of estimations of the volume of the blood (4).

Apart from the exchange of gases, the chemical constitution of the plasma is the most important factor so far as the metabolism of the tissues is concerned. Now the constitution of the plasma is not constant, but, as I shall show, certain changes take place between the corpuscles and the plasma under the influence of the respiratory interchange of gases; consequently a portion of the intercellular substance, being temporarily part of the plasma, comes into the consideration of the metabolism of the tissues.

The plasma carries water, salts, albumens, carbohydrates, and to some degree also fats, for the nourishment of the tissues; the plasma also takes up the waste matter of metabolism, and supplies the material for the formation of lymph and tissue fluids. The complicated processes of absorption and secretion which have not yet been explained on simple physiological lines depend, at any rate in part, on the chemical constitution of the plasma.

The organic constituents of the red corpuscles so far discovered are: hæmoglobin, lecithin, cholesterin, and an albumen which is allied to globulin and coagulates at 75°. The inorganic constituents are: potassium, sodium, calcium, magnesium, chlorine, phosphoric acid, carbonic acid, and water. The plasma consists of serum and of fibrin-forming material. The serum contains the following organic matters:—two albumens—serum albumen and serum globulin; fats, sugar, urea, uric acid, kreatin, carbonic acid, lecithin, cholesterin, and a colouring matter, lutein. The inorganic constituents consist of cholorides, phosphates, and sulphuric acid; of sodium, potassium, calcium, and magnesium.

Hæmoglobin, albumen, and lecithin, with serum albumen, globulin, lecithin, urea, etc., form the nitrogenous matter of the red corpuscles. These can be divided by alcoholic precipitation into two groups, those which are soluble in alcohol—lecithin, urea, etc.; and those which are insoluble in alcohol, *e. g.* albumen and globulin. Each of these substances needs separate consideration as regards its variations in quantity, both in the corpuscles and in the serum, and under both normal and pathological conditions. Our knowledge in this direction is incomplete, but I will mention the most important facts known.

1. Chemical Constituents of the Red Corpuscles.

The literature at our disposal on this subject, with the exception of certain facts about hæmoglobin, is relatively deficient. The first investigations were those of C. Schmidt, but his methods, as was the case with the later ones of Hoppe-Seyler and Jüdell, were inferior to those of Bleibtreu or those made with corpuscular pulp.

The first objection to the method of isolating the corpuscles from the fluid is that the corpuscles are not obtained intact (Aronet, 7). Schmidt used a 3 per cent. solution of sodium sulphate, Jüdell (5) and Hoppe-Seyler (6) a 3 per cent. sodium chloride solution. The same objection applies in a lesser degree to the methods of v. Jaksch (8) and Biernacki (9), who dilute the blood with 1 to 3 per cent. solutions of sodium oxalate to retard coagulation, and who regard the corpuscles which settle spontaneously as unadulterated material. We must provisionally base our knowledge of the chemical constitution of the corpuscles on the analyses of C. Schmidt, which are the most complete up to the present time. I reproduce his table showing the constitution of 1000 gr. of normal human corpuscular substance.

Blood-corpuscles . .	1000	g.
Water . . .	681·63	,,
Non-volatile matter at 12° .	318·37	,,

Hæmatin . .	15·02	(including ·998 iron).
Blood casein .	296·07	
Inorganic constituents	7·28	(excluding iron).

Chlorine . . .	1·750	=	Potassium sulphate .	·132
Sulphuric acid . .	·061		„ chloride .	3·679
Phosphoric acid .	1·355		„ phosphate	2·343
Potassium . .	3·091		Sodium phosphate .	·633
Sodium . . .	·470		Soda . . .	·341
Calcium phosphate .	·094		Calcium phosphate .	·094
Magnesium phosphate	·060		Magnesium phosphate	·060
Oxygen . . .	·401			

Sum of inorganic substances (excluding iron) . 7·282
Density = 1·0886.

This table shows many differences from the constituents of serum (see below). Apart from the large quantity of iron, the relatively small amount of water and great amount of albumen are especially striking. The specific gravity is relatively high. Jüdell in his analyses investigated human and animal blood, but paid special attention to the organic matter. According to Jüdell the following is the constitution of 1000 parts of blood in different species :

	Man.		Dog.	Hedge-hog.	Goose.	Adder.
	I.	II.				
Oxyhæmoglobin . .	867·9	943·0	865·0	922·5	626·5	467
Albumen (and nuclein) .	122·4	51·0	125·5	70·1	364·1	458·8
Lecithin	7·2	3·5	5·9	7·4	4·6	8·5
Cholesterin . . .	2·5	2·5	3·6		4·8	
Other organic matter .	—	—	—	—	—	65·7

According to this table the hæmoglobin is in great excess in the non-nucleated corpuscles of mammals, and the albumens vary inversely to the quantity of pigment.

Schmidt attempted to make similar tables for a few pathological conditions—cholera, dysentery, albuminuria, and dropsy. He found, especially in cholera, that with an increase in the density of the whole blood there was a similar increase in the density of the corpuscles. The density of normal corpuscles is about 1088 ; in cholera it goes up to 1092 or more. In general the increase of density is proportional to the time taken by the processes of transudation. The loss of water is first met by the plasma, which holds the water most loosely, the albumen most strongly, and the inorganic salts in an intermediate condition. A secondary transudation between the corpuscles and the plasma tends to restore their relations, and the blood-corpuscles give up some portion of their contents to the serum. The corpuscles also hold the albumen most strongly, the water most loosely, and the salts in an intermediate condition.

The double stream—first, from the plasma to the capillaries, and secondly, from the corpuscles into the plasma—is summed up as follows:

At the onset water and salts transude through the capillary walls in the proportion of 1000 : 4; the plasma, robbed of a part of its water, then draws water from the corpuscles; the salts in both plasma and corpuscle appear increased absolutely, but diminished relatively to the organic substances. The amount of salts diminishes more and more unless replaced from outside; the chlorine salts of the alkalies, being unnecessary for the functions of the corpuscles, transude into the plasma, whilst the amount of phosphates and potassium salts in the inorganic matter increases at the cost of the sodium chloride which has passed out.

In dysentery and albuminuria, where there are secretions relatively rich in albumens, the amount of salts in the blood increases, but the relative amounts of the salts, and the typical distribution of the potassium and sodium phosphates and chlorides in the morphological elements of the blood, remain unaltered. This relation, however, ceases if the transudation of albumen goes on for years.

To illustrate this I reproduce some of Schmidt's tables:

I. *Cholera.*
II. *Dysentery.*
III. *Albuminuria.*
IV. *Chronic dropsy and albuminuria.*

I. Cholera, man 23 years, at height of disease.

1000 g. blood-cells.

Water	646·17
Material not volatile at 120°	353·83
Hæmatin	20·56 (incl. 3·561 iron)
Blood casein, etc.	324·68
Inorganic material	8·59 (excl. iron)

Chlorine	1·173	=	Potassium chloride	2·467
Phosphoric acid	0·524		„ phosphate	1·210
Potassium	3·121		Potash	1·514
Sodium	1·301		Soda	1·755
Calcium phosphate	0·405		Calcium phosphate	0·405
Magnesium phosphate	1·235		Magnesium phosphate	1·235
Oxygen	0·827			

Weight = 1·1025.

II. Dysentery, girl 18 years.

1000 g. blood-cells.

Water	693·46
Material not volatile at 120°	306·54
Hæmatin	18·89 (incl. 1·256 iron)
Blood casein, etc.	279·80
Inorganic material	7·85 (excl. iron)

Weight = 1·0854.

III. Albuminuria, man 34 years, with œdema.

1000 g. blood-cells.

Water	699·78
Material not volatile at 120°	300·22
Hæmatin	16·80 (incl. 1·117 iron)
Blood casein, etc.	244·29
Inorganic material	9·13 (excl. iron)

Weight = 1·0845.

IV. Chronic dropsy and albuminuria, man 39 years.

1000 g. blood-cells.

Water	703·31
Material not volatile at 120°	296·69
Hæmatin	15·24 (incl. 1·014 iron)
Blood casein, etc.	273·63
Inorganic material	7·81 (excl. iron)

Chlorine	2·226
Sulphuric acid	0·083
Phosphoric acid	1·078
Potassium	2·992
Sodium	0·604
Calcium phosphate	0·197
Magnesium phosphate	0·314
Oxygen	0·320

=

Potassium sulphate	0·181
,, chloride	4·680
,, phosphate	0·969
Sodium phosphate	1·225
Soda	0·248
Calcium phosphate	0·197
Magnesium phosphate	0·314

From these observations it is clear that relations must exist between the serum and corpuscles by which the substances are kept in relative equilibrium as regards their constitution. In this connection Schmidt describes a case of diabetes in which he found a considerable increase in the density of the blood-corpuscles.

These are the most thorough investigations that have been made of the chemical constitution of the corpuscles up to recent times. The first investigation after these of the corpuscular substance was undertaken by v. Jaksch, who employed larger amounts of clinical material. He calculated the amount of nitrogen in the red corpuscles under normal and pathological conditions; but, as I have said, his methods were not entirely free from objection, and consequently his results should only be compared with one another, and not with those of other people who have used a different method. v. Jaksch found between 4·93 and 6·38 g. of nitrogen in 100 g. of humid corpuscular substance, *i. e.* an average of 5·52 g.

In different acute and chronic diseases (pneumonia, typhoid, emphysema, jaundice, nephritis, diabetes mellitus, etc.) the amount also lay between the same limits. In three cases of so-called secondary anæmia (pulmonary tuberculosis, carcinoma of the uterus, nephritis), and in one case of chlorosis, there were relatively small amounts of nitrogen (3·14, 4·01, 4·18, 4·42, and 4·91 respectively).

On the other hand, a case of pernicious anæmia gave a relatively high amount, 5·24 to 6·48 gr. v. Jaksch's results were not constant, possibly because the method was faulty; thus he gives a case of chlorosis in which he found an increase of 56 per cent. in three days. Again, he multiplies the amount of nitrogen by 6·25, and says the product is the amount of albumen. This, of course, as he admits, is quite arbitrary, for not only is the nitrogenous content of human hæmoglobin unknown, but as there are other nitrogenous bodies in the corpuscles, the nitrogen does not depend entirely on the hæmoglobin. Some experiments that I made to find by what number the amount of nitrogen should be multiplied to give the whole amount of albumen, *i. e.* hæmoglobin + globulin (as precipitated by alcohol), gave 8·28 as the average number.

Biernacki's results can also only be compared with one another. He, like v. Jaksch, added sodium oxalate, and examined more especially the constitution of the dried residue. His results are apparently important in many ways; thus he found that hydræmia caused not only a diminution in the number of corpuscles and an increase of water in the plasma, but also an increase of water in the corpuscles, a result which coincides with the observations of Schmidt. Biernacki also found that the normal dry substance of the corpuscles lay between 29·28 and 29·99 per cent.

In a case of carcinoma it was only 27·9 per cent.
" " tabes with anæmia (65 per cent. hæmoglobin) only 25·57 per cent.
" " chlorosis (25 per cent. hæmoglobin) only 22·24 per cent.
" " chronic nephritis (20 per cent. hæmoglobin) only 22·28 per cent.

With regard to the other constituents of the corpuscles in anæmia, Biernacki found that, as a rule, there was an increase of water in the corpuscles, together with an increase of chlorine, which perhaps indicates that with an increase of volume the endoglobular fluid tends to obtain its former concentration. In slight cases of anæmia there was slight increase of potassium, phosphorus pentoxide, and iron; in moderate cases these were normal in amount, and in severe cases diminished. According to Biernacki, potassium, phosphorus, and iron increase or decrease together. In some cases, however, the potassium was diminished, whilst the iron and phosphorus pentoxide were normal. These relations are more prominent when the values for the humid corpuscles are compared with those given by the dry residue. We must, however, notice that when an increase of a substance occurs, it is generally associated with an increased amount of water in the corpuscles. The following table of Biernacki shows the relations of the constituents to the dry residue:

No.	Disease.	Dried, per cent.	In 1 gr. of the dry residue.			
			Cl.	K_2O.	Fe.	P_2O_5.
1	Healthy man . .	28·29	0·0099	0·0082	0·00258	0·00351
2	,, . .	29·99	0·0099	0·0084	0·00251	0·00364
3	Chronic nephritis .	30·43	0·0089	0·0073	0·00262	0·00335
4	Convalescent . .	29·70	—	0·0093	0·00270	0·00363
5	Carcinoma œsophagi	27·90	0·0102	0·0096	0·00297	—
6	Chlorosis	28·07	0·0119	0·0065	0·00262	0·00343
7	Tub. pulm. . .	27·91	0·0099	0·0105	0·00292	0·00436
8	,, . .	26·59	—	0·0090	0·00349	—
9	Chlorosis	26·54	0·0129	0·0051	0·00282	0·00391
10	,, ...	25·84	0·0139	0·0085	0·00279	—
11	Tabes, anæmia . .	25·51	0·0129	0·0092	0·00279	0·00361
12	Ulcus ventric. . .	24·25	0·0129	0·0099	0·00262	0·00559
13	Chlorosis . . .	22·24	—	0·0053	0·00279	—
14	Chronic nephritis .	22·88	—	0·0105	0·00197	—

The amount of iron in the corpuscles, according to this table, generally increases as the amount of dry residue diminishes. As iron is an internal constituent of hæmoglobin (and occurs otherwise only in traces), Biernacki concludes that the corpuscles hold *more hæmoglobin* in anæmia than under normal circumstances; he concludes also, and in this he is supported by Jüdell, that a *diminution of the albumen* in the corpuscles is characteristic of anæmic blood. This suggests that the swollen corpuscles of anæmia may possibly contain the normal concentration of hæmoglobin. It is an interesting result, and seems to me to be important enough to deserve further investigation.

Wendelstadt and Bleibtreu (10), using the method of the brothers Bleibtreu, made investigations on the blood of corpses. Certain facts detract from the value of their results. Thus the number of their cases is insufficient, no normal values are submitted, and the so-called normal saline solution is used for dilution; whilst post-mortem changes, affecting the salts and water-contents, between the corpuscles and plasma have probably taken place (Limbeck, 11). They found the nitrogen of the humid corpuscles varies in different diseases between 5·288 and 7·538 per cent., whilst the nitrogen of a single corpuscle lies between ·000000003477 and ·000000005011 mg. Some observations of my own seemed to confirm Biernacki's results. In two cases of severe anæmia I found the water of the corpuscles somewhat increased (72·1 and 73·4 per cent., the normal being approximately 70 per cent.), and the amount of chlorine rather high (·9 and 1·8 per cent., normal being about ·6 per cent.). No stress can, however, be laid on these results, as the Bleibtreu method which was used is open to many objections.

To sum up, the water is the most variable constituent of the corpuscles: on the one hand, it forsakes them in anhydræmia; on the other, it increases in oligocythæmia. Next to the water the inorganic matter, especially the sodium chloride, is most variable, whilst the albumens or nitrogenous bodies still retain relatively constant values. Similar results are shown in the changes undergone in the red corpuscles in the process of respiration (see below) as regards their variations in the amount of alkali.

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2. The Chemical Constituents of the White Corpuscles and Platelets.

Our knowledge of the composition of the white corpuscles is still very deficient. The fact that we have at present no method of isolating these cells from the blood acts as a bar to the suitable study of the subject, and we are forced either to make deductions from analyses of normal and leukæmic blood, or to rely on analyses of pus, or, as Lilienfeld (1) has lately done, of cells from lymphadenoid tissue.

Hoppe-Seyler (‘Physical Chemistry,’ p. 405) examined leukæmic blood and found formic acid, acetic acid, lactic and glycerin-phosphoric acids; but as he used post-mortem blood, it is doubtful whether these bodies are not products of disintegration of such bodies as lecithin. The amount of lecithin, according to him, is increased in leukæmic blood. The appearance of xanthin bases and of glycogen in leukæmic blood has often been described (Salomon, Nasse, Hoppe-Seyler, and Woroschiloff).

The examination of the leucocytes in pus gives a better idea of the constitution of the white corpuscles; but we must remember that in pus, especially when obtained from old abscesses, the cells are not unaltered, for simple examination with the microscope shows that the pus corpuscles are appreciably different from the ordinary white corpuscles.

The most important organic constituents of pus cells are albumen and nuclein. Miescher (2) thought he could distinguish five kinds of albumen, viz. alkali-albumen; one which coagulated at 48° to 49°; one which was soluble in water and coagulated at 70°; one which was insoluble in water, swelled up in sodium chloride solution, and was soluble in very dilute hydrochloric acid; and one which was dissolved with difficulty in water, salines, and dilute hydrochloric acid. Miescher further found that the pus corpuscle was very rich in lecithin.

Hoppe-Seyler (3) gives the following two analyses of 100 parts of the organic substance of nuclei :

TABLE.

		I	II
Albumen	13·762	68·95	67·369
Nuclein	34·257		
Insoluble residue	20·566		
Lecithin	14·383		7·564
Fat			7·500
Cholesterin	7·400		7·283
Cerebrin	5·199		10·284
Extractives	4·433		

We see that the chief constituents are albumens, nuclein, and the insoluble substances. Miescher (4) gives the following percentage of inorganic constituents in 100 parts of dry pus corpuscles :

TABLE.

Earthy or iron phosphates	0·4160	per cent.
Sodium phosphate	0·6063	,,
Potassium ,,	1·2010	,,
Sodium chloride	0·1428	,,
Organic compounds of phosphoric acid	0·314—0·203	per cent.

Hoppe-Seyler found in 100 g. dry substance—

TABLE.

$ClNa$	0·435
$Ca_3(PO_4)_2$	0·205
$Mg(PO_4)_2$	0·113
$FePO_4$	0·106
PO_4	0·916
Na	0·068
K	trace.

The *large amount of phosphoric acid* in both analyses is striking, and is doubtless dependent on the nuclein. Freund and Obermeyer (5) obtained similar results in examining pus from mastitis and empyema :

TABLE.

Analysis of 100 *g. of dried pus.*

	Mastitis.	Empyema.
Anhydrous phosphoric acid .	24·12	13·21
,, sulphuric acid .	4·27	3·33
Chlorine	20·09	34·07
Potassium	3·64	3·08
Sodium	40·46	43·69
Calcium phosphate . .	5·49	5·53
Magnesium ,, . .		
Iron ,, . .		

A. Kossel (6) has studied the composition of lymph corpuscles from a new standpoint. He found, like his predecessors, that the chief organic constituents are albumens, nuclein, lecithin, and cholesterin. He calls these bodies primary cell-stuffs, on account of their constant appearance in young cells capable of development. Those bodies which appear only in certain cells, and not constantly even in them, he calls secondary cell-stuffs. These are glycogen, protagon, and fats. Appended is a table of the contents of the leucocytes as found by Kossel, from an analysis of the thymus of a calf.

The dry substance of the leucocytes on an average is 11·49 per cent. In 100 parts we have—

TABLE.

Total phosphorus . . .	3·01	per cent.
,, nitrogen . . .	15·03	,,
Albumen	1·76	,,
Leuconuclein . . .	68·78	,,
Histon	8·67	,,
Lecithin	7·51	,,
Fat	4·02	,,
Cholesterin	4·40	,,
Glycogen	0·8	,,
Silver combination of the nuclein bases	15·17	,,

The high amount of nuclein in these cells is a noticeable feature of the analysis, and might be expected when we remember that the nucleus nearly fills the whole cell, if we may judge by the microscope. The nuclein, an organic combination of phosphorus, nucleic acid, and albumen, is combined according to Kossel, both in the nucleated red corpuscles and in the lymph-cells, with another body of albuminoid nature, viz. histon, with which it forms the so-called nucleo-histon. The nucleic acid can become free in the cells under certain unknown conditions; this seems of biological importance, more especially in the study of phagocytosis, for Kossel has shown the bactericidal action of this acid. The fact that the albumens and the nucleic acid are differently affected by Ehrlich's staining fluid, is of interest. The albumens are acidophile, being of a basic nature, *i. e.* they stain with acid dyes (acid fuchsin, eosin): the nucleic acid is basophile, and stains with the basic dyes (methyl blue, green).

The chemistry of the white corpuscles is so far, then, as Kossel says, of a purely descriptive nature; in other words, it describes the substances which temporarily appear in our material, and attempts to discover their relations. The changes which occur in these relations must be left to future investigations. Such changes probably do occur, for Kossel has shown that the so-called nucleins are not equivalent bodies, and that the combination of the nucleic acid and the albumens is of variable stability.

It is obvious that neither physiology nor pathology can gain from our present knowledge of the chemistry of the white corpuscles.

With regard to the constitution of the platelets, our knowledge is still more indefinite. Ranvier (8) finds particles of fibrin in them; Bizzozero (9) considers them as a mixture of two albuminoids: whilst Löwit (10), who denies their existence in the blood-vessels, thinks that they consist of a body allied to globulin. Lilienfeld (11) does not agree with these observers, on account of the results of his digestive experiments. He shows, by artificial pepsin-hydrochloric digestion, that the platelets first become granular and then, after a short delay, differentiated into a pale, homogeneous sphere and a nuclear mass. The latter becomes gradually swollen, pale, and homogeneous, and at the same time the former dissolves away into the fluid. The digestive residue of the platelets forms a lightly nucleated circular body, which swells up on the addition of soda, and is restored to its normal condition by the addition, at the proper moment, of 0·30 per cent. hydrochloric acid. Sodium phosphate acts in the same way as soda. According to Lilienfeld the microchemical reactions of the platelets and of the nuclei of leucocytes are identical. The nuclear mass of the former, as obtained by artificial digestion, consists of nuclein and albumen united together in the form of nucleo-albumen. Fresh platelets are soluble in ammonia, concentrated hydrochloric acid, concentrated nitric acid, ammonium carbonate, dilute caustic potash, and dilute acetic acid; they are insoluble in dilute hydrochloric acid and concentrated caustic potash. They swell in dilute solutions of sodium chlorate, in dilute solutions of soda, sodium phosphate and sodium chloride. The residue left after artificial digestion (nuclein) is soluble in concentrated hydrochloric or nitric acid.

An experiment of Lilienfeld throws some light on these bodies. If we take horse-plasma, filtered in the cold, and containing no platelets, and add under the microscope the sperm of a boar, we see, at first singly, then in great numbers, bodies which are exactly like platelets both morphologically and in microscopic appearance. Lilienfeld, therefore, is inclined to regard the platelets, not as separate constituents of the blood, but as derivatives of the nuclei of the leucocytes. Lilienfeld has shown, by a method invented by himself and Monti, that phosphorus is present in the platelets.

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3. The Chemical Constituents of the Serum.

If blood from a vein is allowed to coagulate, the blood-clot squeezes out a fluid within a few hours; this fluid is called blood-serum. It is yellow, the colour varying in depth, and more or less strongly opalescent according to the amount of fat it contains. Its formation can be accelerated by centrifugalisation. The fluid obtained by coagulation is always clearer than that obtained by defibrination and subsequent sedimentation or centrifugalisation. Again, the constitution of these two forms of serum is not identical. In the first place the defibrinated blood is much richer in corpuscles, and in the second the fluid obtained by coagulation (the blood being obtained from a vein) has the character of venous blood-serum, whilst the defibrinated blood, owing to access of air, has the character of arterial blood.

Each of the constant constituents of serum, which have so often been referred to in the preceding pages, can undergo quantitative changes under physiological and pathological conditions, but our knowledge does not yet cover all these possibilities. The foreign substances in the serum, whether formed in the body or brought in from outside, use the serum partly as a dissolving material, partly as a carrier. The following table of C. Schmidt's gives a general view of the chemical composition of the serum:

1000 g. Serum taken from a healthy man 25 years old.

Water	908·84
Material not volatilised at 120°	91·16
Albumen, etc.	82·59
Inorganic material	8·57

Chlorine . .	3·565		Potassium sulphate	0·283
Sulphuric acid .	0·130		,, chloride	0·362
Phosphoric acid	0·146		Sodium ,,	5·591
Potass . .	0·317		,, phosphate	0·273
Sodium . .	3·438	=	Soda . .	1·545
Calcium phosphate	0·300		Calcium phosphate	0·300
Magnesium ,,	0·220		Magnesium ,,	0·220
Oxygen . .	0·458			

If we compare this with the table of constituents of red corpuscles, we notice the comparative richness in water, chlorides, and sodium, and the poverty in albumen and potassium.

It seems advisable to discuss the constituents separately, and to consider, as far as possible, their variations in pathological conditions.

(*a*) *The albumens of the serum.*—The serum always contains two albumens, viz. serum-globulin and serum-albumen. Chabrié (1) claimed to have found a third, which he called albumon; but Drechsel (2) and Brunner (3) have shown that this substance is not present in living blood, and is due to the coagulation of albumen and globulin. According to Hamarsten (4) the total amount of albumen in normal human serum is 7·6199 per cent. Although the amount of albumen is comparatively fixed, relatively to other substances in the serum, it nevertheless undergoes some small variations in health and disease, whilst the proportion of the two albumens also varies. Becquerel and Rodier (5) made a large number of examinations of serum in health and disease, and summed up their results as to the variations in the quantity of the albumens as follows :

"The albumen of the serum diminishes appreciably in three special conditions, viz. Bright's disease, certain diseases of the heart with dropsy, and puerperal fever."

Schmidt also noted variations—*e. g.* an increase in a case of severe cholera (153·21 in 1000 g. of serum) and a diminution in nephritis (44·21 in 1000 of serum). There is very little in recent literature concerning this subject. Panum (6) found a diminution in starving animals, and concluded that a certain portion of the albumen in serum ought to be considered as material for nutrition. Hoppe-Seyler (7) examined the serum of a case of melanotic sarcoma and found the amount diminished (6·768 per cent.). v. Jaksch (8) and Pick and myself (9) have investigated the subject more recently. v. Jaksch estimated the amount of nitrogen and not the actual amount of albumen, and then indirectly calculated the amount of albumen by multiplying this by 6·25 (König and Kisch, 10); Pick and I (11) have, however, shown that this method is inaccurate.

v. Jaksch's results were as follows:

The amount of nitrogen in healthy serum is on an average 1·37 per cent. In diseases of the nervous system, in poisoning, diabetes, pneumonia, typhoid, septicæmia, and polyarthritis, the amount varies slightly above and below this number. In heart affections and in pleural exudations it rises; whereas it falls in renal diseases. It is also less than the normal in leukæmia, pernicious anæmia, secondary anæmia, and chlorosis.

I defibrinated and centrifugalised blood and examined it after v. Jaksch's method.

I found the following amounts of nitrogen:

TABLE.

Diagnosis.	Nitrogen in serum.	Nitrogen in the alcohol extractives.	Difference.
	Per cent.	Per cent.	Per cent.
Chlorosis I	1·314	0·034	2·5
Chlorosis II	0·996	0·022	2·2
Osteomalacia	1·238	0·025	2·0
Normal	1·153	0·057	4·9
Neuritis	1·018	0·019	1·8
Neuralgia	1·054	0·022	2·0
Emphysema	1·179	0·02	1·6
Nephritis	0·984	0·014	1·4
Uræmia I	0·964	0·104	10·7
Uræmia II	0·984	0·116	11·7

Diagnosis.	Albumen in the serum by weight.	Nitrogen in the serum.	Calculated from the albumen.	Difference.
		Per cent.		Per cent.
1. Pneumonia croup	6·285	1·0143	6·339	0·8
2. Influenza pneumonia	5·056	0·9177	5·737	13·4
3. Emphysema	5·708	1·035	6·468	13·5
4. ,,	9·174	1·545	9·658	5·1
5. Chronic nephritis	7·084	1·365	8·533	21·5
6. Emphysema and albuminuria	8·908	1·176	7·35	17·5
7. Chlorosis	7·55	1·081	6·75	10·8

My values for normal blood are smaller than those of v. Jaksch; thus, in the serum of a case of acute infectious fever, I found no appreciable diminution in the amount of nitrogen. I found, however, that there sometimes was a loss of nitrogen in anæmia, chlorosis, and nephritis.

One thing seems to be certain, viz. that the albumens are relatively fixed in quantity compared with the other substances in the serum. Thus Schmidt found that there was a proportionate increase of albumen in the serum in a case where the blood was distinctly increased in density. v. Jaksch and I have found almost constant values, more especially in infectious fevers. On the other hand, processes connected with loss of albumen, whether through the intestine or kidneys, frequently show a diminution of albumen in the serum; the old relations are, however, gradually restored. It is not possible at present, owing to the paucity of our data, to form conclusions with regard to the variations of the albumen or nitrogen in the serum in processes which are accompanied by oligocythæmia.

The two albumens of the serum, in contrast to the relative stability of their total amount, vary considerably as regards one another. This is true not only for the serum of different mammals, but for the serum of man in normal and pathological conditions. It is not yet decided whether the serum-globulin is a derivative of the serum-albumen, although it has been found possible to produce it from the most dissimilar albumens by putrefaction, pancreatic ferment, caustic alkali, etc. (12).

The following table (13) shows the comparative relations of the two albumens in different vertebrates:

Animal.	Albumens of the blood-serum.		
	Total per cent. of albumen.	Serum globulin.	Serum albumen.
Man	7·62	3·10	4·52
Horse	7·25	4·56	2·67
Ox	7·50	4·17	3·33
Rabbit	7·52	1·78	4·43
Dove	5·01	1·32	3·69
Hen	4·14	2·90	1·24
Tortoise	4·76	2·82	1·94
Lizard	5·16	3·33	1·83
Land tortoise	5·25	4·66	0·69
Snake	5·32	4·95	0·37
Frog	2·54	2·18	0·36
Newt	3·74	8·31	0·43
Eel	6·73	5·28	1·45
Dog-fish	1·62	1·17	0·45

We see that in general the globulin has a relatively higher proportion to the albumen in cold-blooded than in warm-blooded animals. Our knowledge on this subject does not warrant any definite conclusions. Bruckhardt (14) found in dogs, and Tiegel (15) in snakes, that the albumen diminishes and the globulin relatively increases in starvation, but Howells and Salvioli (16) showed that their work was erroneous. Emmerich (17), in the case of rabbits immunised to swine erysipelas, observed that as the globulin disappeared the immunisation increased.

A small amount of work has been done by Estelle (18), Hoffman (19), Halliburton (20), and Mya and Viglezio (21) on the composition of human serum in disease. Estelle's investigations referred especially to the urine of Bright's disease, and are only of service in that he estimated in two cases the albumen and globulin in the serum at the same time. He found in one case 8·5 per cent. total albumen, 3·06 per cent. globulin, 5·44 per cent. albumen; in the other case, 5·4 per cent. total albumen, 1·8 per cent. globulin, and 3·6 per cent. albumen. The investigations of Hoffman involved the relations of the two albumens in the serum and in the ascitic fluid of certain cases. He found variations in the total albumen of 2·96 to 8·51 per cent., whilst the ratio of albumen to globulin varied from ·69 to 1·78. Halliburton says briefly, but without giving figures, that the blood in acute fevers shows an increase of both globulins, *i. e.* of the fibrinogen and serum globulin formed in the plasma. He connects this with the inflammatory leucocytosis which causes an increase of cell globulin. Mya and Viglezio refer especially to the relation of albumen to globulin (the so-called "albuminoid co-efficient") in transudations and exudations, and give seven tables containing the results of their investigations upon the serum with regard to this point. The following is a summary of these :

(I) In disease the relation of the albumen is much altered, the globulin increasing and the albumen diminishing.

(II) These alterations vary directly with those which occur in transudations.

(III) An increase of blood-pressure increases the loss of albumen more than that of globulin.

(IV) Disturbances of circulation cause an increase of the albumen in the exudations.

The results obtained by Pick and myself are given in the following table. The normal relations are—globulin 16·9 to 38·3 per cent. to albumen 61·7 to 83·1 per cent.

Diagnosis.	Per cent. of total albumen. Globulin.	Albumen.
Nephritis chron.	31·4	68·6
,,	9·09	90·9
,,	49·5	50·5
,,	28·6	71·4
,,	36·2	63·8
,,	70·9	29·1
,,	51·6	48·4
,,	32·5	67·5
Stenos. ost. venos. sin.	39·3	70·7
Tumor endothorac.	35·9	64·1
Cirr. hepat.	51·6	48·4
Pneumonia croup.	36·04	63·96

Diagnosis.	Per cent. of total albumen.	
	Globulin.	Albumen.
Pneumonia croup	25·8	74·2
Typh. abd.	38·5	61·5
Icterus febr. . . .	34·9	65·1
,, . . .	17·2	82·8
Pleuritis	74·0	26·0
Erysipelas	37·9	62·1
Meningitis	51·2	48·8
?	32·5	67·5
Pneumonia	44·6	55·4
Diabetes mell. . . .	44·4	55·6
,, . . .	13·3	86·7
,, . . .	16·8	83·2
,, . . .	55·3	44·7
,, . . .	53·9	46·1
,, . . .	41·1	58·9
Carc. uteri	27·2	72·8
,, ovarii . . .	56·1	43·9
Chlorosis	34·53	65·47
Anæmia	38·3	61·7

These facts seem to indicate that the globulin is relatively more resistent in the serum. This is perhaps explained by its smaller diffusibility (Gottschalk, 22); thus in a case of ours of diabetes, the globulin reached 53·9 per cent. of the total albumen; and in other cases of this disease we found relatively small amounts of globulin—in one case only 13·3 per cent., *i. e.* a subnormal amount. As we obtained similar results in other cases we are not in a position to substantiate the above theory.

Halliburton's statement that the globulin is relatively increased in acute infectious fevers is not always true, for in our thirteen cases of acute infectious fevers the globulin varied from 17·2 to 74 per cent.; it is, however, true that the globulin was, as a rule, increased.

Ducceschi ('Centralblatt für Physiol.,' ix, No. 10) has shown that a gradual increase of albumen relatively to globulin occurs after extirpation of the thymus in a dog, until the convulsions come on, and that then the converse holds good.

A few experiments have been made which seem to show a qualitative change in the albumen. Semola (23) showed that the diffusibility of the albumen in Bright's disease was increased, but Dochmann (24) contested this. Freund (25) has lately investigated this question with great care, but his statistics are not sufficiently numerous to give a reliable result. The experiments are, however, interesting, as they open up a new field of view. Another observation of Freund's is very interesting. He finds that if serum or serous fluid is slowly heated, it stiffens into a gelatinous mass at between 70° and 74° C., whilst the serum of Bright's disease does not stiffen—and then the clot is not firm—before a temperature of 78° to 82° C. is reached. At present we cannot give an explanation for this; it is probably in some way due to the diminished percentage of globulin and albumen in the serum. Freund found that in health the relation of globulin to albumen in the serum was about 1 to 1·5, and in Bright's disease 1 to 11·3, *i. e.* comparatively little globulin.

(*b*) *The salts of the serum.*—The qualitative composition of the salts dissolved in the serum is not accurately known, and although its bases and acids have been frequently investigated, we do not know what salts are formed by their combination, what changes occur in the course of metabolism, or whether they cannot be combined, in part, with the organic constituents of the serum. The salts of the serum are alkaline, acid, and neutral, according to their chemical nature; some salts, being chemically unsaturated, must be regarded as acid, although they are capable of combining with acids. The so-called neutral phosphate (Na_2HPO_4) and sodium hydrocarbonate ($NaHCO_3$) are members of this class. The *alkalies*, when not present as neutral salts, are combined with carbonic, phosphoric, and sulphuric acids. Gürber (26) has lately demonstrated the presence of a primary alkali carbonate (both neutral and acid), and has shown that part of the carbonic acid in the serum is combined with the lime, kept, he thinks, in solution by the hydrocarbonate (acid carbonate) present. The *phosphoric acid* apparently forms combinations with all the bases present, for the neutral and acid phosphates in the serum being the predominant compounds, a portion of the phosphoric acid present originates (as in the whole blood) from those organic combinations present which contain phosphorus, viz. lecithin, cholesterin, and nuclein. These are present, however, only in small quantity, and the chief part of the phosphates are of inorganic origin. The *sulphuric acid* seems to be chiefly combined with sodium. The *bases* present, in order of percentage amount, are sodium, potassium, magnesium, and calcium (ammonia see below). *Sodium and potassium* are present for the most part in the form of chlorides, but partly as carbonates and phosphates.

The physiological *rôles* of the two groups of salts, the neutral and alkaline, are, as far as is known, different. The latter form an alkaline reservoir for the physiological acid formation in the tissues, and as such are of vital importance. The former (chlorides) are also indispensable to the body, but we do not yet know in what way. Our knowledge concerning the variations in the amount of phosphates and chlorides in the serum is extremely small and unsatisfactory; it is possible that there is some relation between the percentage of phosphates and the percentage of chlorides (Limbeck, 27; Biernacki, 28).

(*c*) *The amount of water in the serum* compared with the total amount of the whole blood is fairly constant, and Hammerschlag (30) has shown, in over four hundred cases, that the specific weight of the serum is also fairly constant.

(*d*) *The colour of human serum,* obtained by spontaneous coagulation, is for the most part yellow, with a slight strain of green. The fluid is distinctly fluorescent. Serum obtained by centrifugalisation is somewhat reddish, owing to the fact that it contains some red corpuscles. Our knowledge of the pigment of normal serum is scanty. Hamarsten (31) and others consider it to be identical with bile pigment. Krukenberg (32) and others class it amongst the so-called lipochromes. The pigment of human serum gives the same reactions as that of other warm-blooded animals, *e. g.* cattle. It is soluble in alcohol and ether, and gives a blue reaction with iodine and sulphuric acid. If we examine normal serum with the spectroscope we see a gradually increasing darkness of the spectrum from the light blue to the violet, which remains unaltered on the addition of reducing and oxidising substances. In jaundice this darkening is intensified, and its commencement in the blue is more distinct.

The natural colour of serum may alter under pathological conditions. This is due to the passage of bile or hæmoglobin into the plasma, and occurs also when substances (*e. g.* methyl blue) are artificially introduced into the blood. The presence of bilirubin in the serum is easily shown (v. Jaksch, 33) in simple obstructive jaundice, and in excessive secretion of bile. The colour varies from orange-yellow to brownish yellow according to the amount of bile pigment. Bilirubin is also present in the serum in cases of so-called "urobilin icterus" (A. v. Jaksch, 34). Unaltered hæmoglobin in any quantity is less frequently found in the serum. If destruction of red corpuscles takes place from any cause in the vessels (hæmoglobinæmia), the fate of the hæmoglobin dissolved in the plasma depends on the degree of activity of the liver cells which tend to change the hæmoglobin into other pigments.

The stromata of the destroyed corpuscles collect in the spleen (Ponfick, 36). We get hæmoglobinæmia and hæmoglobinuria if the capacity of the liver is exceeded in this direction. Hæmoglobinuria, therefore, indicates a very considerable destruction of red corpuscles. This may be due to two causes, viz. diminished resistance of the corpuscles and abnormal chemical relations of the plasma. The former occurs (Lichtheim, 36; Murri, 37) in so-called *paroxysmal hæmoglobinuria,* and Chwostek (38) claims to have found that in these cases the red corpuscles exert a "deficient resistance" towards mechanical influences. This is also said to occur in the case of burns (Silbermann, 'Virchow's Archiv,' Bd. cxix, p. 88). The second cause, viz. an increased destruction of normal red corpuscles, due to some abnormal chemical change in the blood, occurs in cases of *poisoning* with so-called blood-poisons, and in many pathological conditions in which the power of the serum to break up these globules is increased. Maragliano (39) deserves the credit of having directed attention to this property of serum. The blood-corpuscles of healthy persons are *not* broken up when transferred to the serum of other healthy persons. If, however, they are transferred to the serum of invalids they are often quickly broken up, and, what is especially remarkable, their pigment disappears completely. The serum does not show the colour of hæmoglobin, but is green and yellow, and, as is shown by the spectroscope, contains hæmatoidin. This is an important fact, for, in the first place, it proves that hæmoglobin can be altered without the intervention of the liver; and secondly, it explains a certain change of colour in serum that has not yet been touched upon.

In certain diseases the serum becomes strikingly green, so much so that it is initself sufficient evidence that a patient is severely ill. In these cases the serum is almost grass-green, is very strongly fluorescent, and spectroscopically shows hæmatoidin. I have observed this especially in pneumonia, typhoid, and purpura hæmorrhagica. Maragliano has observed an increase of the globucidal action of the serum on red corpuscles in anæmia, carcinoma, lead poisoning, leukæmia, purpura, cirrhosis of liver, nephritis, pneumonia, malaria, typhoid, erysipelas, and tuberculosis. In addition, Hans Buchner (40) and Castellino (41) have investigated the existence of the globucidal power of the serum of different animals on the corpuscles of others, and of the serum of patients upon the corpuscles of healthy men. The first two believed they had found a connection between this power and the amount of salts in the serum, for serum poor in salts shows a heightened globucidal power, whilst the addition of salts decreases it.

Buchner and later Castellino have shown that relations exist between the globucidal and bactericidal action of serum. It is known that the serum of healthy animals has certain toxic effects on the serum of a different species. These are shown not only on intra-venous but also on subcutaneous or intra-peritoneal injection, and lead to coagulation and breaking up of red corpuscles. Human serum has this effect on rabbits (Mairet and Bosc, 42). In general 15 c.c. of human serum is enough to kill a 2-lb. rabbit. The serum loses a portion of its virulence and of its coagulating power on being heated to 52°—53° (Mairet and Bosc), or

55°—58° (according to Hayem [43]), or on the addition of a small amount of salts (sodium chloride and sodium sulphate), so that the toxicity of serum does not depend only on its coagulating power. This has also been shown by intraperitoneal injections (Leclanché [40] and Reymond [44]). Mairet and Bosc, and Hayem considered that the poisons in the serum consisted of albuminoids. Castellino, on the other hand, has lately shown that all the toxic qualities, the globucidal, the coagulating, and the toxic powers increase and decrease together, and all depend on the amount of nuclein. It has also been shown that, just as the serum of animals is of different virulence according to the species (in the case of rabbits human serum is more poisonous than the serum of dogs), so the serum of patients is generally more poisonous than the serum of healthy men.

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4. THE CHEMICAL CONSTITUTION OF THE BLOOD AS A WHOLE.

C. Schmidt found the following substances in 1000 g. of blood taken from a healthy man twenty-five years old:

TABLE.

Water	788·71 g.	
Material not volatilised at 120°	211·29 g.	
Hæmatin	7·70	(incl. 0·512 iron)
Blood casein, etc.	151·89	
Fibrin	3·93	
Albumen, etc.	39·89	
Inorganic matter	7·88	(excl. iron)

Chlorine . .	. 2·62	=	Potassium chloride	. 2·062
Sulphuric acid .	. 0·094		Sodium ,,	. 2·701
Phosphoric acid	. 0·766		Potassium sulphate	. 0·205
Potassium .	. 1·739		,, phosphate	1·202
Sodium .	. 1·902		Sodium ,,	. 0·921
Calcium phosphate	. 0·193		Soda . .	. 0·457
Magnesium ,,	. 0·137		Calcium phosphate	. 0·193
Oxygen . .	. 0·427		Magnesium ,,	. 0·137

Becquerel and Rodier give the following percentages in healthy *males*, based on eleven separate examinations of 1000 g. of blood :

TABLE.

	Average.	Maximum.	Minimum.
Density of the blood . .	1060·2	1062	1058
,, serum . . .	1028	1030	1027
Water	779	760	800
Nuclein	141·1	152	131
Albumen	69·4	73	62
Fibrin	2·2	3·5	1·5
Extracts and salts . . .	6·8	8·0	5·0
Fats	1·6	3·255	1·0
Seroline	0·02	0·08	Trace
Cerebrine	0·488	1·00	0·27
Cholesterine	0·088	0·175	0·03
Soaps	1·004	2·00	0·70
From 1000 gr. calcined blood :			
Sodium chloride . . .	3·1	4·2	2·3
Soluble salts	2·5	3·2	2·0
Phosphates	0·334	0·7	0·225
Iron	0·565	0·633	0·508

Becquerel and Rodier give the following percentages in healthy *females*, the result of eight investigations of 1000 g. of blood :

TABLE.

	Average.	Maximum.	Minimum.
Density of the blood	1057·6	1060	1054
,, serum	1027·4	1030	1026
Water	791·1	773	813
Nuclein	127·2	137·5	113
Albumen	70·5	75·5	65
Fibrin	2·2	2·5	1·8
Extracts and salts	7·4	8 5	6·2
Fats	1·62	2 86	1·0
Seroline	0·02	0·06	Trace
Cerebrine	0·464	0·80	0·25
Cholesterine	0·09	0·2	0 025
Soaps	1·046	1·8	0·725
From 1000 gr. calcined blood :			
Sodium chloride	3·9	4·0	3·5
Soluble salts	2·9	3·0	2·5
Phosphates	0·354	0·65	0·25
Iron	0·511	0·575	0·486

Biernacki found in four healthy persons of middle age the following values for 100 g. of blood :

TABLE.

	Age.	Dried residue.	Cl.	KCl + NaCl.	K_2O.	Na_2O.	Fe.	P_2O_5.
1. Healthy man	25	22·3	0·468	0·646	0·157	0·210	0·0566	—
2. ,, ,,	35	22·82	0·456	0·684	0·174	1·216	0·0519	0·0729
3. ,, woman	25	22·5	—	—	—	—	—	—
4. ,, ,,	25	23·22	0·441	0·633	0·160	0·200	0·0568	—

I obtained the following results in three males in 100 g. :

		Case I.	Case II.	Case III.
Density		1055	1061	1058
Nitrogen	vol. per cent.	2·62	3·21	3·06
Sodium chloride	,,	·73	·65	·728
Dry residue	,,	20·98	24·01	21·94
Water	,,	84·61	82·07	82·85

A. The Water.—The Density of the Blood.

The specific weight of the blood depends on the quantity of dry substances and water it contains. The amount of water in the blood is regulated in physiological and pathological conditions by the tissues; thus if the tissues have lost large amounts of water (*e. g.* in perspiration or diarrhœa), then more water than salts leaves the blood. Water is the most variable of the constituents of the blood. The inorganic salts appear to be more constant, and the albumens still more so; so that in the most serious losses of water the density of the blood increases. The increase of density, however, is not as great as the diminution of volume. When fluid containing organic and inorganic substances is added to the body, the water leaves the body before and to a greater degree than the salts, and appears as relatively dilute urine. It is only when the amount of salts added is considerable, and that of water relatively small, that part of the inorganic matter is at once eliminated through the kidneys. The necessary water for this purpose is provided by the tissues; consequently the tissues are deprived of water before the blood (Grawitz [1]). The water takes the first place in the excretions, and the inorganic constituents of the blood the second. Certain organic constituents of the tissues and the blood are on the same level as the inorganic bodies, *e. g.* urea, which is a constant component of the urine, but is normally found only in minute quantities in the blood. The albumens of the blood have the greatest difficulty in passing through the capillary walls and the kidneys, whilst the water and the salts leave the vessels together. It is necessary for different salts to have a certain minimal concentration in the blood, in order that the processes of secretion by the epithelial cells of the kidney may be stimulated.

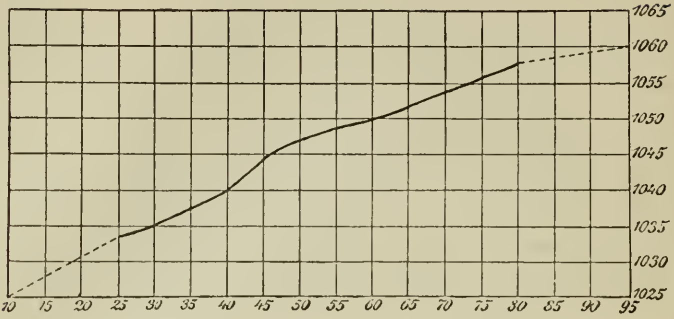
These constituents of the blood have the same relative difficulty in leaving the vessels under pathological conditions. The water, therefore, is the most variable constituent of the blood, whilst the inorganic substances, and especially the albumens, are more constant. The easily diffusible chlorides vary more than the phosphates. The water in the blood is the sum of the water in the corpuscles and that in the serum, making allowance for their volumes. Now the solids in the serum are much less than those in the corpuscles, consequently the greater the amount of serum in blood the greater the amount of water; such an abnormal increase is called *hydræmia*. An increase in the volume of plasma is therefore a condition of hydræmia, but this is not its only cause, for an increased amount of water in the serum and in the corpuscles can also produce it. If the converse condition obtains—that is, if the amount of water in the blood (whether the result of relative deficiency of plasma or abnormally small amounts of water in the plasma or in the corpuscles) is diminished—we get a thickening of the blood, or anhydræmia, a condition which is caused by withdrawal of water from the body.

Hydræmia and anhydræmia are, within narrow limits, physiological, and can be brought about by a draught of water or a vapour-bath. The regulatory apparatus is promptly brought into play, in the first instance by the action of the kidneys, and in the second by the feeling of thirst. These variations are marked by differences in the density of the blood, while the rapidity of compensation may be taken as a criterion of the osmotic relations between the blood and tissue fluids. The *specific weight of the blood* depends chiefly on the amount of the dry substances it contains; the specific weight, however, does *not* vary directly with the amount of dry substances, though it does so approximately (Stintzing and Gumprecht [2]). Hammerschlag (3) and Siegl (4) have shown, also, that the amount of hæmoglobin often varies directly as the density. We know that the red corpuscles are the heaviest component of the blood, and the hæmoglobin the chief part of the red corpuscles, therefore these small variations can be explained by variations in pathological conditions, and, especially in anæmia, in the quantity of the albumens, to say nothing of the inorganic salts. Nevertheless it is certain that small transitory differences of density are proportional to the amount of dry residue and to the hæmoglobin.

The amount of water in the blood is given by Becquerel and Rodier as being on an average 77·9 per cent. in healthy males, and 79·1 per cent. in females. Stintzing and Gumprecht give these values as 78·4 and 80·2 respectively. The relative hydræmia of females is a confirmed fact, and is caused apparently by menstruation, as there is no hydræmia in female children and old women (Stierlin).

The physiological and pathological variations in the specific weight of the blood, as shown by means of simple methods adapted for clinical use, have lately been the subject of much discussion; in addition to the old statements of Davy, Nasse, Vierordt, Becquerel, Rodier, and Landois, we have the later work of Roy (5), Lloyd Jones (6), Devoto (7), Hammerschlag (8), Schmaltz (9), Peiper (10), Scholkoff (11), Siegl (12), Hock and Schlesinger (13), Glogner (14), Schlesinger (15), Menicanti (16), Grawitz (17), Lyonnet (18), and Moeli (19). The normal figures of these authors vary a little according to the methods used. Thus Becquerel and Rodier give the variations of specific weight in healthy males as 1058—1062 (average 1060·2), and females 1054—1060 (average 1057·6); Hammerschlag, 1056—1063; Lloyd Jones, 1035—1068; Peiper, 1045·5—1066·5; etc. All the authors find a relatively smaller specific weight in women after puberty. All the physiological influences on the specific weight of the blood can be explained by the difference of intake and excretion of water, and the capacity for the tissues of taking up water. Lloyd Jones, in investigating the influence of *age* on the density of blood in health, found the specific gravity to be highest at birth (1066) in both sexes; between the second week and second year the density sank to a minimum (boys 1048—to girls 1050); it then gradually increased, reaching its highest in males between the thirty-fifth and forty-fifth year (1058·5), and in females after the climacteric (1054·5). The period of childbirth is generally characterised by a relatively low specific weight. The density increases in old age, in both sexes, until the initial density of birth is again reached. Fig. 19 shows the curve of density after Siegl (omitting early childhood).

FIG. 19.



THE SO-CALLED POLYCYTHÆMIA OF THE NEW-BORN, and the increased density of the blood, is caused by the great loss of water undergone at birth. In early childhood the capacity of the tissues for taking up water is very considerable, and causes, when water is imbibed, a relative richness in humidity of the tissues, and therefore of the blood. In later life, about the fiftieth year, the power of the tissues for taking up water begins to lessen, and consequently, other influences being absent, the density of the blood increases.

Solid and fluid food must evidently affect the density of the blood; thus Schmaltz gave ·6 per cent. sodium chloride solution, and the density sank from 1059·7 to 1057·4. He examined his own blood at intervals for ten weeks, and found the following averages at different times:

O'clock . . .	7—8	8—11	11—2	2—5	5—8
Specific weight .	1060·9	1060·0	1058·8	1058·8	1058 8

—showing that the daily variations were chiefly dependent on the absorption of food.

Müntz (20) showed that the CONDITION OF NUTRITION affected the density. In fat sheep the density was 1058, in ordinary sheep 1038. The dry residue of the former was 20·33, of the latter 13·6 per cent. MENSTRUATION, according to Schmaltz, causes a slight thickening of the blood (1054 to 1057·2), and PREGNANCY and confinement a slight thinning.

MUSCULAR EXERCISE causes a slight diminution of density, and SLEEP a slight increase (Lloyd Jones). The INFLUENCE

OF CLIMATE on the condition of the blood is of special interest. Glogner found that the specific weight in twenty healthy Europeans, living in Sumatra, was lower (1047·5—1057·3) than in our latitudes. Glogner, in view of the fact that these men had a normal number of corpuscles, thinks that this was due to a hyp-albuminosis of the blood. The opposite condition seems to obtain in HIGH ALTITUDES. Thus Müntz, with reference to Viault's (21) observations, found—

In rabbit on the Pic du Midi (2877 m. high) specific weight 1060·1 — on plain 1046·2.

In sheep on the Pic du Midi 1053·2 — on plain 1038·0.

The probable causes of these and analogous blood changes in high altitudes will be discussed later.

Lloyd Jones and Scholkoff have made observations which seem to show that the density may vary in different parts of the circulation, but this does not appear to me to be proved. The slight variations found are perhaps dependent on the portion of the body from which the blood was taken being covered by clothes or not. COLD increases, HEAT decreases the density; PERSPIRATION increases, WARM APPLICATIONS and INHALATION OF AMYL NITRITE diminish it (Grawitz). The loss of density in different forms of oligocythæmia is explained by the relatively increased volume of the serum. When this loss of density does not occur, or is small in amount, *e.g.* in chlorosis and other clinical forms of anæmia, the amount of dry substances or of corpuscles in the blood sufficiently explains the change. In such cases hæmoglobin plays the chief part. Hammerschlag, Siegl, and others, as we have seen, laid stress on the parallelism between the density and amount of hæmoglobin; but Stintzing and Gumprecht showed that they were not invariably proportional. According to these authors the dry substances of the blood are reduced in chlorosis in greater degree than the number of red corpuscles.

The great extent to which the density can sink in severe oligocythæmia has been often shown; thus a density of 1040 or even 1030 is not uncommon. In a case of pernicious anæmia, I found a density of 1031 (number of red corpuscles 1,227,000; volume of serum 92·41 per cent.; dry residue 8·47 per cent.). Krüger found the dry residue in two cases of anæmia, due to loss of blood, to be 9·39 and 9·41 per cent. The alterations of density in certain forms of chronic cachexia are harder to interpret, *e. g.* the inconsiderable diminution of specific weight in leukæmia, in which, as in other cases where an oligocythæmia of the red corpuscles does not occur at the same time, we should expect an increase. Thus Peiper notes values of 1054·6 and 1039, Copemann of 1048·5 and 1051. Leukæmic blood has, of course, a somewhat higher amount of dry substances than is indicated by its amount of hæmoglobin, and affords the most striking instance that the indirect variation of the water and the amount of hæmoglobin is only conditional; for here the hæmoglobin diminishes, but the amount of water does not increase, whilst the other albumens increase in quantity.

The observations of the density in TUBERCULOSIS are fairly extensive, but do not seem to conform to any uniform rule. Thus Lloyd Jones finds the specific weight always diminishes, whilst Peiper says it increases, and Scholkoff found it to be sometimes normal and sometimes slightly diminished. Grawitz (22) gave an explanation of these observations; he said that in the first stage of phthisis there was anæmia and loss of density, but that in a later stage the density became approximately normal, whilst in the third stage it again became subnormal. The change in the concentration of the blood between the first and second stages, when the tubercular infiltrated tissue begins to break up, is striking, and Grawitz tried to elucidate it by the following experiment:—Extracts (made by Heidenhain's method) of tubercular matter were subcutaneously injected into a rabbit with these results:

	Specific weight.	Dry substance.	Dry substance of the serum.
5.20 p.m.	1045	17·05 per cent.	7·5 per cent.
5.29 ,,		Injections made.	
5.33 ,,	1046	18·10 per cent.	
5.38 ,,	1048	18·40 ,,	7·7 ,,
6.0 ,,	1049	18·40 ,,	8·0 ,,

An extract of tubercular matter, therefore, caused the blood to become concentrated. In the later stages of phthisis, when we have a pyogenic infection, the diminution of density is due to the fact that water enters the vessels from the tissues for the absorption of the products of these germs. This theory is interesting, and may be true, but in practice no doubt other influences, *e. g.* sweats, etc., come into play. Variations of the blood-density also occur in the course of *syphilis*, especially when under treatment with mercury (Letzius [23], Jeleneff [24], Loos [25], Bieganski [26]).

ERUPTIONS OF SKIN DISEASES (pemphigus, eczema, psoriasis, prurigo, morbus maculosus) and BURNS often have an undoubted influence on the concentration of blood (Schlesinger). In the former, the loss of nutrition (and eventually of blood) plays a part. In burns a considerable increase of density has been observed (Tappeiner [27], Baraduc [28], Schlesinger), but this generally disappears in forty-eight hours. The values in such patients are exceptionally high (1065—1073, Schlesinger). Such high numbers are occasionally obtained in certain other conditions, *e. g.* congenital heart disease. On these grounds Tappeiner suggested that death from burns was due to concentration of the blood, but Czerny (29) has shown that the concentration is of no pathological importance. We cannot at present come to any conclusion with regard to the cause of the concentration in burns and skin diseases, as the fluid withdrawn from the vessels is hardly sufficient to explain it. Grawitz by his experiments on the action of tubercle has, perhaps, indicated the real reason.

Most observers find an almost constant diminution in the density of blood in the fatal cachexia of MALIGNANT DISEASE. Thus Lyonnet found in carcinoma of stomach 1045, 1042, 1040, 1032, and 1037. The accompanying loss of blood (*e. g.* from uterus or stomach) may, of course, lead to dilution of the blood, but malignant tumours seem to cause a diminution in the density apart from this. Grawitz found that injection of cancer material diminished the density of blood, but inasmuch as it was not proved that the poison was present in the vessels, and as his observations are few in number, we cannot say for certain that the loss of density is due to the attraction of water into the blood-vessels.

Acute congestion is generally accompanied by more or less increased density, provided that an existing albuminuria or nephritis does not prevent it. These relations are reduced in chronic disturbances of the circulation by the accompanying œdema, and so we get different results in HEART DISEASE; thus Bamberger (31) found that the specific weight was increased; Hammerschlag that it was normal, whilst Schmaltz frequently found a diminution. Later observations of Stintzing and Gumprecht showed that the amount of water in the blood was increased in uncompensated cases, and that when compensation was established, the water became normal in quantity. A diminution in density undoubtedly occurs in the majority of cases of BRIGHT'S DISEASE, as Bright himself showed. Hammerschlag investigated a large number of cases, and frequently found normal values in chronic interstitial nephritis, whilst in parenchymatous nephritis, he always found a diminution, although the hæmoglobin was often nearly normal. This observation indicates a relative addition of water to the serum or to the blood-corpuscles. Oligocythæmia is apparently out of the question, and it seems to me that this addition of water to the serum may be due to two causes: first, the relative loss of albumen of the serum; and secondly, the overloading of the tissues with water. Neither of these conditions, however, necessarily causes thinning of the blood, for, as we have seen above, albuminuria can occur without causing loss of density, and without any loss of the albuminoid contents of blood, whilst œdema can exist without causing any dilution of the blood (v. Jaksch [32]).

In ACUTE INFECTIOUS DISEASES there is no fixed law as regards the density of the blood. Grawitz has investigated the action of the products of several micro-organisms, but the conditions are so complicated in different diseases and in different stages of each disease, that the action of the products of the specific organisms, even if constant, are overshadowed. Streptococci, according to Grawitz, cause an increase of the fluid in the vessels; in pneumonia, however, even when it is due to streptococci, the density often increases. This is sufficiently explained by the expectoraiton and the profuse perspiration which occur at the crisis. In typhoid the copious evacuations tend to cause concentration of the blood, and act against the effects of the micro-organisms which tend to produce a dilution of the blood. There is no regular law in other diseases, *e. g.* diabetes, gout, rickets, osteomalacia, etc. The concomitant circumstances, *e. g.* anæmia or kidney affections, may deprive the blood of any characteristic it otherwise might have, so that the original disease may appear to have no influence on the density of the blood.

If pathological circumstances affect the density, whether by the intestines, or skin, or vaso-motor mechanism, it is *a priori* probable that similar effects are caused by INTOXICATIONS, OR DRUGS, *e. g.* APERIENTS OR DIURETICS.

The actions of a large number of medicinal substances on the density of blood have been observed, *e. g.* mercury by Schlesinger, Bieganski, and others; phosphorus by Taussig (33). I found that carbon monoxide led to an increased density of the blood, and Münzer (34) and Arthur Latham have shown that the number of red corpuscles is increased in coal-gas poisoning. Bieganski and Schlesinger found that injections of sublimate at first increased and then diminished the density. On the other hand, inunctions and injections of oil of cinereum had no influence. Subcutaneous applications of benzoate of mercury and the yellow oxide of mercury caused an increase of hæmoglobin and so of the density (Jeleneff). Many drugs, on the other hand, do not influence the density at all.

Summary.—The density and the amount of water of the blood in physiological and pathological conditions undergo considerable variations. The tissues and their power of absorption have an intimate connection with the quantity of water in the blood. The action of the vaso-motor centre has a considerable effect on the density. The most important point in pathological cases, so far as the density is concerned, is the amount of plasma in the circulation.

B. The Albumens of the Blood.

The albumens of the blood consist of the albumens of the corpuscles and of the plasma. The amount of albumen depends chiefly on the amount of hæmoglobin, as the amount of albumen in the serum is relatively small, and as the hæmoglobin forms nine tenths of the organic substances of the corpuscles; consequently the greater the proportion the corpuscles bear to the whole blood, the greater is the amount of albumen. This holds good, however, only in comparisons of two kinds of blood, in which the corpuscles show no noteworthy difference in chemical constitution.

An estimation of the total albumen in the blood is of subordinate value. According to C. Schmidt, the amount of albumen of the whole blood (*i. e.* hæmatin, blood casein, etc., fibrin, albumen, minus iron) was in two normal cases 198·29 and 166·341 g. for 1000 g. blood; according to Freund and Obermeyer (37) it is 19 per cent., whilst v. Jaksch (35) found 3·62 per cent. of nitrogen in healthy blood, which, according to his method, would give 22·62 per cent. of albumen. The amount of nitrogen was approximately normal in diseases of the nervous system, diabetes, and cases of poisoning, but diminished in acute fevers such as pneumonia, typhoid, and septicæmia. It was normal in diseases of the heart, lungs, and pleura; often reduced, sometimes normal, in renal diseases; whilst in leukæmia, pernicious anæmia, and chlorosis it was always diminished. Secondary anæmias also usually showed a diminution, but occasionally the nitrogen was normal in amount. v. Jaksch considers that the amount of nitrogen varies indirectly as the amount of plasma, the dry residue and amount of albumen being approximately proportional, owing to the relatively small quantity of salts in the blood. This relation is not, however, always constant (Stintzing and Gumprecht).

When we speak of the albumens of the blood we mean, in addition to the hæmoglobin, the globulin-like substance of the red corpuscles, the serum-albumen, and the serum-globulin; but there is reason to think that in certain pathological circumstances, such as leukæmia, other albumens appear in the blood. E. Ludwig (38), Freund and Obermeyer (39),

v. Jaksch (40), and lately Matthes (41), have described such bodies; the first three assert that a peptone is present in the blood of leukæmia. Matthes claims that he has found a deutero-albumose. It is possible, considering that until lately the nomenclature of the products of albuminous digestion was uncertain, and in view of the processes the observers used to separate the bodies in question, that what were considered to be peptones were really albumoses, or even that they were not original constituents of the blood, but were produced from the albumens by the chemical processes used. It is a striking fact that all the observers who found peptone or albumoses in leukæmic blood used post-mortem blood, and that Devoto (42) and Wagner (43), who examined the blood during life, found neither of these bodies. It seems obvious that the peptone and albumoses are post-mortem appearances. v. Jaksch (44) found peptone in a case of leukæmia during life. I examined the blood taken during life from a leukæmic case, and divided it into two parts. I examined one portion at once and found neither peptone nor albumose; whilst the other, which was allowed to stand for forty-eight hours, contained an albumose. Again, it is well known that if albumose is present in the blood it quickly appears in the urine, but Stadelmann and Senator have found albumose uniformly absent in the urine of leukæmia.

Freund (45) finds peptone a constant constituent of the blood in sarcoma, but absent in carcinoma. The fact that peptones and albumoses are often found in urine in the most widely different diseases, seems to indicate that small amounts of these substances or other hydration-products of albumen may sometimes exist in the fresh blood of living people. Chabrié (46) states that he has found albuminoids in pneumonia and nephritis which were neither peptone nor albumose. I have found albumoses in cases of pneumonia, catarrhal jaundice, and in erysipelas. Martin (47) and Matthes found peptones and albumose-like substances, post mortem, in the blood of children who had died from diphtheria.

C. THE OTHER NITROGENOUS SUBSTANCES OF THE BLOOD.

If we can judge by the amount of nitrogen, other nitrogenous bodies besides albumen must be present in the blood. Of these urea is the most important. The urea in the blood increases when it is not excreted by the kidneys. According to Gescheidlens (48) it is also increased in fever. In uræmia the nitrogen of the urea can reach ·1—*i. e.* the urea may amount to ·4 per cent. of the serum. Uric acid exists in normal blood, but only in traces. Garrod (50) showed that it was increased in acute attacks of gout (·25—·175 per cent.); Salomon (51) showed an increase in pneumonia and anæmia; and Abeles (52) demonstrated its presence in 187 g. of normal blood. v. Jaksch, taking blood by venesection, found urea in appreciable quantity in those suffering from dyspnœa (whether due to heart disease or other causes), in pneumonia, nephritis, and severe anæmia. He thinks its presence is due to failure of oxidation (dyspnœa or want of hæmoglobin). Against this view we have Kraus's (54) gas analyses, which show that the respiratory co-efficient, $\frac{CO_2}{O}$, in severe anæmia is the same as it is in health, so that there is no question of failure of oxidation in these cases.

Klemperer ('Deutsch. med. Woch.,' 1895) found—

3 Normal cases . .	0· uric acid
1 Leukæmia . . .	·0985 per cent.
1 Pneumonia . . .	0·
1 Contracted kidney .	·0685
1 Uræmia . . .	·1065
1 Acute gout . . .	·067—·0915 and ·088
1 Gouty kidney in the uræmic stage . .	·44

Weintraud found that the uric acid in one case amounted to ·007 g. in 140 g. blood, after the administration of calf's sweetbread. Ammonia was stated to be present in dog's blood by Brücke (55), but this was denied by Bichlmayer (56). The presence of a trace of this substance in human blood is probable, as it is well known to be a regular constituent of urine. The fact that in certain conditions (acute infections, intoxications) it leaves the body in increased quantities (Hallervorden [57]) is of importance, especially in reference to Walter's (58) theory of acid poisoning in fever, etc. Hoppe-Seyler (59) thought that ammonia might be formed during the experiments by micro-organisms, but this contingency is easily avoided. Lupu made some observations in my laboratory which indicate that traces of ammonia exist in the blood and in the serum. A condition of ammonæmia, *i.e.* poisoning by ammonium carbonate, has been described (Treitz and Jaksch [60]) and is based on Frerich's theory of uræmia. Frerich supposed that ammonium carbonate was formed in uræmia out of the urea of the blood, and then caused poisoning. It was suggested that the kidney was normal in ammonæmia but that the urine was decomposed in the body owing to cystitis or other causes, and that ammonium carbonate was formed and absorbed. But now that Frerich's theory is given up, and ammonium carbonate is known neither to have the poisonous qualities attributed to it, nor to be formed in the body in any quantity, the theories of ammonium carbonate poisoning, both in uræmia and this so-called ammonæmia are merely of historic interest. The name ammonæmia has been given by other authors to a different condition—a supposed ptomaine poisoning. When urine was shown to contain poisons, it was supposed that such toxic substances were formed in stagnating urine and absorbed. v. Jaksch, jun. (62), states that he has convinced himself of the truth of this, but has not yet published his observations. For the present, therefore, ammonæmia is not a definite pathological condition.

With regard to the other nitrogenous bodies in blood, viz. the so-called xanthin bases, we have the older experiments of Scherer, Mosler, Salkowski, and Salomon (63), whilst v. Jaksch (64) has written concerning the appearance of hypoxanthin. He found in certain pathological conditions, not only varying amounts of uric acid, but also xanthin bases especially xanthin and hypoxanthin. Creatin (65) and carbamic acid (66) have been described as being present in the blood of animals, but, as far as I know, have not received consideration as constituents of human blood. Nencki (67) has found carbamic acid in the blood after extirpation of the liver.

D. The Ash of Blood.

The ash represents the sum of the non-volatile inorganic constituents of blood. The volatility and constitution of the salts depend of course on the composition of the serum and the corpuscles. An analysis of the ash alone gives no satisfactory idea of the division of the inorganic substances in the blood.

C. Schmidt found the dry residue to be 17·5 per cent., the inorganic matter ·9 per cent., *i. e.* the latter formed about 5 per cent. of the total dry residue. Of the inorganic substance iron accounted for ·0489 per cent., the other inorganic constituents of the corpusples ·0355 per cent., and the inorganic constituents of the plasma ·507 per cent. In a second case the dry residue was 21 per cent., the inorganic constituents ·839 per cent., *i. e.* 4 per cent. of the dry residue, of which ·374 per cent. belonged to the red corpuscles, ·0512 per cent. to iron, and ·414 per cent. to the plasma. The values vary in pathological cases. In cholera Schmidt found that the inorganic matter varied between ·67 to 1 per cent., but that its relation to the dry residue was nearly constant, 3·1 to 3·5 per cent. The inorganic matter is constantly decreased in comparison with the organic, as the salts are more diffusible than the albumen. This is seen in the action of laxatives on the blood, whilst the contrary is found in cases of Bright's disease, for here the inorganic matter forms a relatively larger percentage of the dry residue; in one such case it rises to 6·5 per cent., obviously owing to the comparative poverty of the blood in albumen. Schmidt's results of his analyses in two healthy cases are as follows:

TABLE.

	Case 1.		Case 2.	
	In 1000 g. blood.	Per cent. of ash.	In 1000 g. blood.	Per cent. of ash.
Chlorine	2·62	31 %	2·845	27 %
Sulphuric acid	0·094	1 ,,	0·089	0 ,,
Phosphoric acid	0·766	9 ,,	0·506	5 ,,
Potassium	1·739	21 ,,	1·612	17 ,,
Sodium	1·902	22 ,,	2·564	28 ,,
Calcium phosphate	0·193	2 ,,	0·418	4 ,,
Magnesium phosphate	0·137	1 ,,		
Iron	0·512	6 ,,	0·489	5 ,,
	8·392		9·109	

Jarisch examined ('Wien. med. Jahrbücher,' 1877) four normal cases and one case of pneumonia, and obtained the following results:—

TABLE.

	Normal per cent.	Pneumonia per cent.
P_2O_5	8·82	8·61
SO_3	7·11	11·44
Cl	30·74	28·63
K_2O	26·55	22·92
Na_2O	24·11	26·06
CaO	0·90	1·24
MgO	0·53	0·50
Fe_2O_3	8·16	7.03

We see that chlorine, potassium, and sodium, are the most important constituents of the ash, and that the earths and acids are of subordinate value. Differences amounting to as much as 6 per cent. of the total ash occur even in healthy cases. Traces of other substances are found, *e. g.* lithium, fluorine, lead, copper, manganese. The constituents of the blood must differ according as the individual, from whom the blood is taken, has reached adult life or not. In the latter case it is self-evident that the salts necessary for the formation of the bones, muscles, etc., must be supplied to the body. Bunge (68) has shown that the body is richer in potassium and poorer in sodium during growth. Milk contains the necessary salts in sufficient quantity, with the exception of iron. The significance of the inorganic salts of the tissues and blood in the adult is quite different from that of the organic. The latter serve as sources of strength, the former, however, release no energy on breaking down. The inorganic substances are, nevertheless, necessary for life, and we find that if they are not supplied the amount excreted in the urine is diminished. Forster (69) and Lunin (70) have shown the vital importance of the salts to the nutrition of dogs, pigeons and mice, and that when food is withheld death is due to the want of salts. Lunin thinks he has proved that death is due to acid-poisoning (the formation of sulphuric acid from the sulphur of the albumen), but this does not seem to be certain. We are not able to say why the salts are indispensable. Bunge thought that this need of salts depended, in herbivora, upon the richness of their food in potassium, and that the potassium in the body caused an increased output of sodium in the urine. Schenk (71) and Landsteiner (72), however, published investigations which showed that this occurred, if at all, only for a short time. Schenk fed rabbits with food free from chlorine, and found that the amount of chlorine in the blood sank on the first day but then rose again. In dogs too, when the chlorine was withheld for nineteen days, the amount of chlorine in the blood decreased only by from ·297 to ·283 per cent.

Landsteiner fed a number of young rabbits on hay, and a similar number on cow's milk, for three and a half months. In the latter case be found ·783 Na_2O and 3·778 of K_2O in 1 g.; in the former the relation was as 1 to 9·6. No appreciable difference in the blood occurred in these experiments. It follows, therefore, that the food usually contains an excess of the salts required, and that the body takes what it requires and discards the rest.

Our knowledge is very scanty concerning the special physiological significance of the separate salts in the blood and tissues. We, however, know the properties and quantitative changes of some of them, and we also know that a certain saline concentration is necessary to keep albumens in solution, and that phosphates, according to their constitution, may be capable of combining with acids or bases. Again, the importance of iron in hæmoglobin is well known.

The following is an example of an ash-analysis in a case of cholera in a girl of 20 (l. c., p. 44).

TABLE.

	In 1000 g. blood.	Per cent. of ash.
Chlorine	2·21	27 %
Phosphoric acid	0·612	6 ,,
Sulphuric ,,	0·17	2 ,,
Potassium	1·66	20 ,,
Sodium	1·724	21 ,,
Calcium phosphate Magnesium ,,	0·325	4 ,,
Iron	0·863	10 ,,
Total	8·113	

On comparing this with the normal table we see no appreciable change except a distinct increase of iron, which may be due to concentration, as the specific weight was 1060·9. In another of Schmidt's cases, a man thirty-nine years old, with chronic dropsy and albuminuria, the following results were obtained :

TABLE.

	In 1000 g. blood.	Per cent. of ash.
Chlorine	3·312	38 %
Sulphuric acid	0·167	1 ,,
Phosphoric ,,	0·486	5 ,,
Potassium	1·162	13 ,,
Sodium	2·334	27 ,,
Calcium phosphate	0·269	3 ,,
Magnesium ,,	0·278	3 ,,
Iron	0·347	4 ,,
Total	8·667	

The increase of chlorine and sodium and the decrease of iron and potassium are striking, but easily explained. The diminution of iron shows a relative poverty of red corpuscles, and so of potassium. The corresponding increase of plasma causes an increase in sodium and chlorine.

An analysis of the blood of a case of diabetes in a man thirty-four years old gave the following numbers:

TABLE.

	In 1000 g. blood.	Per cent. of ash.
Chlorine . . .	2·765	33 %
Sulphuric acid . .	0·172	2 „
Phosphoric „ . .	0·502	6 „
Potassium . . .	1·703	20 „
Sodium	1·861	22 „
Calcium phosphate . .	0·354	4 „
Magnesium „ . .	0·018	0·2 „
Iron	0·583	7 „
Total . .	8·333	

Although there was apparently no decrease of red corpuscles there was a slight increase of chlorides, whilst the amount of potassium and of sodium was considerable. The case of pneumonia, quoted above, shows loss of chlorine and at the same time an increase of sodium, so that in this case the last-named is not caused by an increased volume of the plasma. The increase of calcium (increase of fibrin formation) is striking.

Freund and Obermayer (74) examined a case of leukæmia, in which they demonstrated the presence of peptone, and obtained the following results:

TABLE.

In 100 parts ash:

	In leukæmia.	Normal (Jarisch).
Anhydrous phosphoric acid .	16·92	8·82
Anhydrous sulphuric „ .	12·31	7·11
Chlorine	17·82	30·74
Potassium . . .	15·65	26·55
Sodium	38·52	24·11
Calcium	0·47	0·90
Magnesium . . .	0·07	0·53
Iron oxide . . .	2·24	8·16

The potassium, chlorine, calcium, and magnesium, were therefore diminished, and the sodium and pentoxide of phosphorus increased. This is explained by a relative deficiency of red corpuscles and increased number of white corpuscles, for Obermayer found a relative diminution of potassium in pus compared with sodium and pentoxide of phosphorus.

Kohler (75) gives a case of osteomalacia.

TABLE.

In 100 parts ash:

	In osteomalacia.	Normal.
P_2O_5	7·25	8·49
SO_3	16·04	6·85
Cl	19·925	29·59
K_2O	34·16	25·565
Na_2O	9·35	23·169
CaO	0·25	0·872
MgO	—	0·512
Fe_2O_3	12·85	7·86

We have then an increase of potassium and iron, and a diminution of chlorine and sodium, which probably indicates a relative increase of red corpuscles, *i. e.* a deficiency of plasma. The increase of sulphuric acid is remarkable.

The variations of the chlorine in the blood are much greater than those in the serum, owing to the very variable amount in the corpuscles. My observations show that the amount of sodium chloride in the blood varies in disease between ·39 and ·906 per cent. In health the values are not constant; thus C. Schmidt found the values in health to be ·43—·47 per cent. by weight; Becqueral and Rodier found in males an average of ·31, and in females an average of ·39 per cent. by weight. My own values are somewhat higher, probably on account of the fact that I only charred the blood, and did not reduce it to ashes; thus I found in three healthy men an average of ·7 vol. per cent. (·73, ·65 and ·72), and in three females ·64 per cent. (·66, ·65, and ·62). Biernacki gives the chlorine value in health as ·441 and ·468 per cent. which reckoned as potassium and sodium chloride is equivalent to ·633—·646 per cent. Becquerel and Rodier have collected most of the material for an estimation of the amount of chlorine under pathological conditions. They find that blood-letting increases the relative amount of sodium chloride, *e. g.* from ·28 to ·34 per cent.; that the amount of salt is relatively high in chronic anæmia and in typhoid (·35 per cent.), but in inflammations and phlegmasias approximately normal. In chlorosis the average was also normal, but varied considerably in separate instances (·26—·39); whilst in tubercle and syphilis it was high. These values, in consequence of the faults of our present methods, are all too low, but they show that the greater the amount of serum compared with that of the blood, the greater is the amount of sodium chloride—*i. e.* the richer blood is in water the greater the amount of chlorine (Biernacki [76], Moraczewski [77]). The relatively small volume of serum, with its smaller amount of salt, causes the abnormally small chlorine values in pneumonia. Biernacki in one case of this disease found that the chlorine value was ·385 per cent.; Schenk gives ·314 per cent., whilst I examined three cases and obtained the results ·39, ·39 and ·422 vol. per cent. sodium chloride. In erysipelas the same thing holds, but the values are a little higher; thus I found in three cases, ·39, ·45, ·45 vol. per cent. In typhoid my observations show that the oligoplasmia which is present is the cause of the low chlorine values, for the serum gave a normal amount, whilst the blood gave low ones (·401—·548 per cent. sodium chloride). Oligocythæmia generally shows a high sodium chloride value, on account of the relative polyplasmia. The effect is sometimes heightened by the corpuscles and serum containing increased quantities of chlorine; thus I found in a case of pernicious anæmia ·819 per cent. in the serum, and ·897 vol. per cent. sodium chloride in the blood. A case of chronic parenchymatous nephritis with anæmia gave ·822 in the serum and ·906 in the blood. Biernacki obtained similar results in six cases of chlorosis—that is a diminution of the number of red corpuscles and very high volumes of chlorine in the blood. All anæmias do not show this relation; this I was able to show especially well in two cases of chlorosis. The blood in these cases was typically chlorotic, and the amount of chlorine in the serum was normal but the sodium chloride in the blood was diminished. In the one case the sodium chloride in the serum was ·625 per cent., and in the blood ·397 per cent. In the other it was respectively ·596 and ·514 per cent. This diminution was due to the poverty of the corpuscles in sodium chloride. Biernacki gives similar results. The statement that polyplasmia is accompanied by an increase of chlorine is usually true, but there are exceptions. There is a relative poverty of sodium chloride in the blood of jaundice. In four cases of tubercle the chlorine was somewhat low; carcinoma gave great differences (·374—·509 per cent.). In five cases of chronic nephritis it was shown that the greater the anæmia the greater the amount of chlorine. These clinical facts are few in number and should be corroborated by further clinical evidence. We can only, as we have already said, deduce the rule that the richer the blood is in chlorine, the greater the amount of plasma or serum it contains, and this is not always true. Landenheimer (77) has recently described a retention of chlorine in cases of carcinoma, and he professes to show that when water is retained, the corresponding salts are also retained, so as to form a "physiological" salt solution.

The chlorine in the whole blood is combined with sodium rather than with potassium. The total of both potassium and sodium chloride is, according to Biernacki, about 6 per cent. of the blood-weight, and can increase and decrease in pathological conditions. The amount of alkalies increase when there is an increased amount of water in the blood, on account of their connection with the chlorine. They can, however, increase without an increase of the chlorine, and may decrease or be normal when the water is increased.

Biernacki gives the following example:

TABLE.

	H_2O.	KCl + NaCl.	K_2O.	Na_2O.
	Per cent.	Per cent.	Per cent.	Per cent.
Chlorosis . . .	89·36	0·617	0·061	0·275
Nephritis parench. .	80·52	0·461	0·110	0·151
,, chron. .	81·06	0·556	0 140	0·176
Tuberc. pulm. . .	80·76	0·556	0·134	0·181
Gastritis atroph. .	76·63	0 472		
Carc. pancr. et hepat.	79·71	0·508		

The relatively high proportion of potassium in the corpuscles causes a diminution of potassium in all those cases in which the corpuscles are relatively diminished; consequently deficiency of potassium is not, as Garrod (78) suggests, a peculiarity of scurvy. A diminished amount of potassium generally means an increased amount of sodium. Biernacki gives the following examples:

TABLE.

Case.		No. of blood-cells.	K_2O.	Na_2O.
1.	Healthy man .	4·23 mill.	0·157 per cent.	0·21 per cent.
2	,, ,, .	5·03 ,,	0·174 ,,	0·216 ,,
30	Anæmia graviditas .	0·905 ,,	0·024 ,,	0·348 ,,
29	Cirrh. hep. anæmia .	1·486 ,,	0·056 ,,	0·347 ,,

Biernacki considers that sodium is the most variable constituent of the blood. This is due perhaps to the fact that sodium is combined not only with chlorine but with phosphoric and carbonic acids. He compared the amounts of phosphoric acid and potassium as follows:

TABLE.

	P_2O_5	K_2O
Normal blood .	0·0729 per cent.	0·174 per cent.
Rheumatism .	0·0671 ,,	0·155 ,,
Chlorosis . .	0·056 ,,	0·127 ,,
Tub. plm. . .	0·0601 ,,	0·128 ,,
Tabes, anæmia .	0·054 ,,	0·16 ,,
Carc. ventriculi .	0·0419 ,,	0·099 ,,

The loss of phosphoric acid seems therefore to go with loss of potassium *i. e.* with loss of red corpuscles. In leukæmia we get an increase of phosphorus pentoxide, owing to an increase in the white corpuscles, and in spite of the loss of potassium and increase in sodium. Iron occurs in men in traces in the plasma, and its amount in the blood depends on the amount of hæmoglobin. The normal amount of iron is about ·056—·058 per cent. in human blood; in females it is somewhat less. We should *a priori* expect a parallelism between the amounts of iron and potassium, on account of their connection with the red corpuscles.

Biernacki gives the following figures:

TABLE.

	K_2O.	Fe.	Hb (Fleischl).
Normal blood	0·164 per cent.	0·0551 per cent.	105
Chlorosis .	0·104 ,,	0·0461 ,,	60
,, .	0·061 ,,	0·0223 ,,	25

This relation between the iron and potassium does not always hold good, for iron is found only in the corpuscles, whereas potassium is also present in the plasma; nor does Biernacki's *a priori* assumption that the iron varied directly with the hæmoglobin hold good, as the values of iron were proportionately higher. This fact appears to be largely due to the unreliability of our colorimetric methods.

The amount of calcium and magnesium in the ashes have seldom been observed clinically. Schmidt found the sum of both in health to be ·067—·1018 per cent. reckoned as phosphates. My own observations seem to show that there is on the average more calcium in the old than in the young; but the differences are inconstant and I lay no stress on them.

E. THE CARBOHYDRATES OF THE BLOOD.

The appearance of sugar in the blood in health and disease has often been noticed. The sugar present is grape sugar, or maltose or both. Hofmeister (79) has shown that milk-sugar is present in the urine of suckling women, so it must be assumed that in these cases it is present in the blood. It has not yet been ascertained how the sugar is distributed between the corpuscles and plasma. Hamburger assumes that the red corpuscles of the arterial blood contain sugar. The amount of sugar in the serum of venous blood seems to be somewhat more than it is in that of arterial, but there appears to be no regular difference in the amount of sugar in the venous blood, taken as a whole, as compared with that in arterial.

v. Mering (80) found 0·171 per cent. of grape sugar in the carotid blood of a dog, and ·15 per cent. in the jugular of the same animal; on another occasion ·143 and ·151 per cent. respectively; whereas Chauveau and Kaufmann (81) have stated that venous blood is always poorer in sugar than is arterial. The ingestion of large quantities of sugar in the food and muscular exercise influence the amount of sugar in the blood. Seegen, Chauveau, and Cavazzani (82) agree that muscular exercise diminishes the quantity of sugar. Chauveau's deduction—that sugar forms the combustion material for active muscle—does not hold good. The amount varies with the quantity and quality of the sugar in the food, within certain limits. v. Mering found in dogs:

TABLE.

	Sugar in carotid blood. per cent.
After 44 hours' starvation . .	0·15
,, 48 ,, ,, . .	0·145
,, 5 days' ,, . .	0·133
,, large quantity of sugar . .	0·125
,, ,, ,, . .	0·235
,, bread diet	0·130
,, flesh ,, ...	0·115

We see that starvation causes a slight diminution of sugar, and food, especially carbohydrate food, an increase. As the physical influences mentioned are continually at work, it is difficult to give the normal amount of sugar. I found, *e. g.* ·075 and ·089 per cent. sugar in the venous blood of two healthy young men, between 11 and 12 a.m., *i. e.* about five hours after the last meal. We of course cannot lay any stress on the amount of sugar found in the blood in pathological conditions, unless this is supported by a large number of very accurate observations. Freund was the first to mention pathological differences of sugar in the blood (except in diabetes). He found that a few (2—3) c.c. of blood from a case of cancer (the albumen being precipitated with caustic potash) could reduce copper sulphate; and as this did not occur in other patients, he assumed that it was due to the presence of a comparatively large quantity of sugar. Trinkler (84) has made a large number of estimations of sugar and gives the following table :

TABLE.

Disease.	Average.	Maximum.	Minimum.
	Per cent.	Per cent.	Per cent.
Carcinoma	0.1819	0·3030	0·1023
Typhus abd. . . .	0·095	0·1022	0·0875
Pneum. croup. . .	0·0943	0·1092	0·0813
Dysentery	0·0838	0·0915	0·0796
Morbus cordis . . .	0·0737	0·0897	0·0664
Peritonitis	0·0701	0·0917	0·0450
Tuberculosis . . .	0·0653	0·0817	0·0450
Syphilis	0·0553	0·0748	0·0449
Nephritis.	0·0489	0·0559	0·0311
Uræmia	0·0375		

Freund's statement that the blood in cancer is exceptionally rich in sugar is confirmed. There is also the interesting fact that the amount of sugar is greatly diminished in renal disease, and especially in uræmia.

The differences in the other diseases are too small for any conclusions to be drawn. The cause of the hyperglykæmia in cancer is not yet clear; we might argue that it was due to a failure of oxidising processes caused by the cachexia, but Kraus's experiences show that there is no failure of oxidation, and secondly, other severe forms of cachexia show a diminution in the amount of sugar. Freund finds no sugar in the blood in cases of sarcoma. Cantani (85) found ·5—·8 per cent. of grape sugar in diabetes, Hoppe-Seyler (86) ·9 per cent., and Seegen (87) ·78 per cent. These values seem high, but they are infinitesimal compared with the amount of sugar which is frequently passed in twenty-four hours. Grape sugar is an excellent diuretic when injected intra-venously, and is consequently found in relatively small quantities in the blood, as is the case with other substances, such as urea and sodium chloride, which have a similar action. Many theories have been suggested to explain the presence of sugar in the blood in cases of diabetes, but our knowledge on the subject is very limited. It has long been known that any sugar which may be present in living blood gradually diminishes after the blood has been shed. Mering and Minkowski have also shown that complete extirpation of the pancreas produces not only glycosuria but true diabetes. On these two facts a theory of diabetes pancreaticus has been built up and supported in a series of investigations by Lépine and his pupil Barral (89). These authors assert that the blood contains a ferment—"ferment glycolytique"—which causes the sugar to disappear from the blood outside the body, and that this ferment is formed in the pancreas. It follows, then, that if we extirpate the pancreas of animals there should be a smaller diminution in the amount of sugar present in the shed blood. Lépine (90) proved that this was so in the following experiment:—intense glycosuria appeared twenty-four hours after the pancreas of a dog, which had previously fasted for thirty-six hours, had been extirpated. Arterial blood was taken from the animal and also from a healthy dog, and these specimens were examined immediately after defibrination (A), half an hour later (B), and fifteen hours later (C), with the following results:

	A.	B.	C.
Healthy dog	·117 per cent.	·11 per cent.	·072 per cent.
Diabetic ,,	·33 ,,	·323 ,,	·304 ,,

The loss of sugar therefore was—

In the healthy dog .	6 per cent.	39 per cent.
,, diabetic dog .	2·2 ,,	8 ,,

The *"pouvoir glycolytique"* of the blood in a healthy man is on an average 25 per cent. in one hour (Lépine), but is diminished in diabetes. This author found the following values (91):

Table.

Disease.	Amount of sugar pro 1000 parts.		Percentage loss.
	Estimated immediately.	Estimated after one hour.	
Pneumonia I	1·2	·78	35
„ II	1·04	·78	25
Uræmia	1·00	·77	23
Obesity	1·17	·89	24
Diabetes I	5·07	4·9	3·3
„ II	4·54	4·47	1·6
„ III	3·48	3·23	7·0
„ IV	2·17	2·05	5·5
„ V	3·38	3·30	2·1

This theory of Lépine has been shown to be incorrect: (1) Minkowski (92) found that the *"pouvoir glycolytique"* of a dog whose pancreas had been extirpated was undiminished; (2) Kraus (93) showed that the absolute amount of sugar that disappears in a certain time is about the same in normal and in diabetic blood (as can be seen in Lépine's own data); and (3) Seegen (94) and Arthus (95) have shown that the sugar-destroying power of blood is a post-mortem phenomenon, and is certainly not a vital process.

The breaking up of sugar appears to depend more on the red corpuscles than on the plasma, but it is only one of many changes, which occur in the blood post-mortem (Salkowski [96]). The Lépine-Barral theory consequently falls to the ground. It is self-evident that other diseases, with glycosuria, besides true diabetes, show an increase in the amount of sugar in the blood. In some cases, *e.g.* the so-called alimentary glycosurias, the increase of the amount of sugar is easily understood. Those cases of transitory glycosuria so common after poisoning with carbon monoxide, chloroform, curare, etc., are explained with greater difficulty. In these cases the formation of sugar in the liver appears, experimentally, to be not only not increased, but actually diminished. We must seek the cause in some alteration in the metabolism of the sugar. Seegen (97), Araki (98), Zielessen (99), and Sauer (100) have the same opinion with regard to the glycosuria produced by morphia, amyl nitrite, cocaine, hydrocyanic acid, and curare.

Attention has lately been directed, especially from the clinical standpoint, to the appearance of glycogen in the blood. Many authors (101) have found this substance in the blood of dogs, but some (Salamon, Naunyn) think that it is only present in the leucocytes. Huppert (102) has lately proved its existence in the blood and pus of dogs. Ehrlich (103), then Gabritschewsky (104), and later Livierato (105) used the micro-chemical test of "iodine-rubber" on dried blood. Gabritschewsky claims to have found glycogen in varying quantity in health and disease in both intra- and extra-cellular states. The extra-cellular glycogen is said to be due to the destruction of leucocytes; it is often found enclosed by disintegrated masses of these cells, and is stained a mahogany brown by the iodine. Gabritschewsky also attempted to show, experimentally, that glycogen is formed by the leucocytes in the circulation from grape sugar as well as peptones. Livierato found small globules of glycogen in small masses in normal blood, whilst in disease he found both extra- and intra-cellular glycogen. He considers that the glycogen is increased when an active local process has taken place in cases of fever, or when peptonisable exudations or inflammatory leucocytosis have occurred. Thus glycogen is present in considerable quantities in croupous pneumonia, albuminuria and peptonuria, whereas in cases of typhoid, where there is no leucocytosis, we find but small quantities of glycogen, and this chiefly of the extra-cellular kind. Little glycogen was found in cases of diabetes mellitus. Czerny (106) has investigated this point, and has confirmed the assertion that there is a connection between the number of leucocytes and the amount of matter which stained brown with iodine. The endocellular iodine reaction, together with considerable leucocytosis, was obtained in all cases of pus-formation. It was also found in certain cachectic conditions in children. Czerny has further shown experimentally that when the temperature of the body is lowered there is no increase of this substance in the blood, but that the leucocytes show a distinct reaction after twenty-four hours. Trambusti (107) observed that this reaction becomes marked when the cœliac plexus has been removed, but this may probably be explained by the previous observation of Czerny. Disturbances of respiration (cutting the vagus on both sides), anæmia, and septic suppurations cause increase of this substance in dogs. Czerny made the interesting observation that the substance hitherto called glycogen gave amyloid reactions with iodine and sulphuric acid, and methyl-violet, and was consequently not glycogen, but possibly its antecedent. It has long been known that blood had the power of diastatic action; that is to say, the power of forming sugar out of starch and glycogen. Lépine and Barral (108) and Bial (109) have lately re-directed attention to this matter. The latter showed that starch was converted into maltose and dextrin by this ferment, and laid stress on the sugar-forming power of the serum. Lépine and Barral studied the quantitative variations of this power under different physical and pathological conditions; they found that glycogen is quickly changed into sugar in fresh venous blood provided that the sugar-destroying ferment is absent, and assert that more sugar is formed if the ductus Wirsungianus is tied, or the pancreatic nerves cut. They maintain that after a long period of asphyxia this ferment is increased, and after a short one diminished; that it is also increased in "phloridzin diabetes;" and finally, that the ferment is contained wholly in the serum. Cavazzini (111) examined this ferment later, and found that arterial serum had greater power than venous serum. His observations chiefly affected the circumstances that increased or checked the action of the hæmo-diastase. Small changes in reactions, such as are brought about by the addition of acids or alkalies, hinder its action. This is greatest at temperatures of 30°—38° C.; at 40° it diminishes, and at 75° vanishes. Cavazzini bases a theory, with regard to the heat-economy of the body, upon the action of this ferment in man. Thus if a considerable quantity of powerful ferment is present in the tissues, the body-heat must be increased; but when this increase occurs the power of the ferment diminishes, and consequently the amount of combustion again becomes less. The body-heat is therefore kept approximately stable under physiological conditions.

1 c.c. of plasma placed in 50 c.c. of starch paste produced the following amounts of sugar in the blood in different animals:

Calf	0·103 grain.
Ox	0·115 ,,
Rabbit . . .	0·100 ,,
,, . . .	0·092 ,,
Dog	0·16 ,,
,, ...	0·171 ,,
Cat	0·111 ,,
Pig	0·277 ,,
,, ...	0·491 ,,
Hen	0·155 ,,

Human serum has on the average a weaker diastatic power than that of animals. Castellino and Pracca (112) found the average amount of sugar formed in healthy serum to be ·07 per cent. In the majority of diseases (anæmia, chlorosis, leukæmia, pleurisy, pneumonia, malaria, nephritis, cirrhosis, carcinoma, and cerebral hæmorrhage) the diastatic power was increased. Other diseases (diarrhœa, pericarditis, acute rheumatism, gonorrhœal arthritis, catarrhal angina) gave normal or even subnormal values. They think that in general the severity of the disease causes an increase of diastatic power, and that this depends on the globulicidal power, the coagulating power, and the virulence of the serum. The sugar-making power of serum is increased by contact with the coagulum, nuclein neutralises it, sodium chloride and sodium sulphate increase it, whilst it is diminished considerably by anything that hinders the coagulating process. The authors believe that the leucocytes are the origin of the diastatic ferment.

The appearance of FAT (lipæmia) and fat-like drops in the blood in health and disease has often been observed. The amount of fat can, of course, vary within wide limits (Gumprecht, 113). People who are particularly well nourished and many healthy people often show an increase of fat in the blood after a good meal.

In the days of venesection the amount of fat was often found to be increased even in debilitated conditions (phthisis, nephritis, etc.).

Lipæmia, then, exists physiologically. Whether it has any pathological significance seems to be doubtful. The chief cause of its appearance is no doubt increased ingestion of fat in the food, together with a diminished combustion of fat. We have no data, but it is certain that lipæmia is often found in conditions of diminished oxidation (*e. g.* in drunkards).

The appearance of fatty acids and their products, *e. g.* acetone, has been noticed. As regards the fatty acids v. Jaksch (114) has made some statements that need corroboration. He finds that fatty acids are present in the blood in infectious fevers (febrile lipacidæmia), and thinks that other diseases showing an increase of fatty acids in the urine, *e. g.* diabetic coma, leukæmia, acute yellow atrophy, etc., also show this condition. How far this is true, and whether other volatile substances found in the urine (acetone, etc.) exist in the blood in appreciable quantities is not yet proved, although it appears indubitable that they may be found in the circulation as products of metabolism, and that they leave the body with great rapidity.

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5. The Volume of the Blood-corpuscles and Plasma in the Blood.

The total volume of the red corpuscles is certainly of great importance to the metabolism. The volume of the white cells, on the other hand, is of secondary interest. The greater the volume of the red cells (and, other things being equal, the greater the volume of a single cell), the greater the total surface undergoing oxidation in the lungs. C. Schmidt (1) showed in his celebrated work, that variations of the water of the blood affected both the plasma and also the corpuscles, but pathologists were loth to take the possibility of variations in the volume of the individual corpuscles into account. For instance, Daland (2) wanted, after the appearance of Blix-Hedin's hæmatocrit, to substitute estimations of the volume in place of enumeration of the cells, thereby assuming the identity and constancy of the individual cells. This mistake was also made by Niebergall (3), but Gärtner (4) now came forward and suggested the possibility of variations in the individual cells. This was confirmed by Friedheim (5), who showed that the total volume of the corpuscles was independent of their number and of the amount of hæmoglobin. Herz (6) was the first who undertook to investigate this point under pathological conditions. Before this, Bleibtreu (7) and Bleibtreu and Wendelstadt (8) had cast doubt upon the trustworthiness of deductions of volume estimated by the hæmatocrit and its modifications, and the brothers Bleibtreu (9) had suggested a new method. The discussion as to the comparative value of individual methods has been kept up to the present day, and we can sum it up by saying that none of them are worthy of much confidence. Seeing that the methods are full of error, and that the methods of counting the corpuscles are also liable to error, we may get a double error when we calculate the average volume of a single cell (Pfeiffer, 10). This objection holds good for all estimations founded on a combination of the hæmatocrit and enumeration.

All these circumstances compel us to exercise caution in considering the results of individual observers. A comparison between them is impracticable, because hardly any two use the same methods. We are therefore driven to give the results of each author separately, remembering always that these results are not accurate, and are only of relative value. The total volume of red corpuscles in normal cases was given by Daland as 44—66 per cent. in males (36—49 in females), by Gärtner as 42—48 per cent., by Herz as 40—50 per cent., and by Friedheim as 47—60 per cent.

These results were obtained by centrifugalising. The following results were obtained by the Bleibtreu method:—Wendelstadt and Bleibtreu (11), who unfortunately used only post-mortem blood, found the volume to vary from 25·15 to 49·1 per cent. (and including cases of anæmia from 9·52 to 49·1). Pfeiffer, using fresh blood, obtained values 34·5—55·8 per cent.

We see that the results given by Bleibtreu's method are all smaller than those obtained by the centrifugalising method. This is partly due to the facts already discussed, that Bleibtreu uses normal saline solution to dilute the blood, and that the more concentrated the solution used the greater the volume of the corpuscles.

From these estimations and the enumeration of the corpuscles we can deduce the average volume of an individual corpuscle. Welcker by another method made this volume approximately 772 C. (C. = 1-10,000,000,000 c.mm.; Daland and Friedheim made it 1300 C. and more; Herz 800—1000 C.; Pfeiffer 810—896 C. in males, and 710—950 C. in females; whilst I obtained the value 480—610 C.

As we have said, we must lay no stress on estimations of variations of the individual corpuscles, but must limit ourselves to the alterations of the volume of the plasma which constantly recur, and can be shown by different methods. If we get a case where the volume of the plasma varies and the number of corpuscles remains constant, then we may deduce something about the individual corpuscles. Such a case occurs when we take two portions of the same blood and shake one with oxygen and the other with carbonic dioxide. All methods show (Limbeck, 12; Gürber, 13) that the volume of the serum in carbonic dioxide blood is diminished, *i. e.* there is an increase in the volume of the individual red cells. The fact that all the different methods, however inaccurate their absolute values, lead to the same conclusion, justifies us in recognising this result. Any results which deal with the volumetric relations in different individuals must be accepted with great caution. No stress can be laid on the absolute values found, but if the same methods be used we may compare two specimens. In infectious fevers I found a relative oligoplasmia (volume of corpuscles 31·1—59·3 per cent.; whereas in normal blood I found 24·5—28·6 per cent.). These figures do not seem to prove that a diminution of plasma always takes place in fever; I have myself found only 19·3 per cent. volume of red corpuscles during a rigor in a case of hepatic abscess, although there was distinct oligocythæmia. Still it seems that oligoplasmia is often present in high fevers. This reminds us of Herz's (14) previous observation, that an "acute swelling" of the red corpuscles occurs in acute infectious fevers. Herz, *e. g.*, calculated the average volume of red corpuscle in a case of typhoid as 1090 C., and ten days later as 1003 C. In a case of peritonitis he found it to be 1029 C.

In conclusion we must mention an appearance which constantly occurs, whatever the method of volume estimation. This is the increased volume of red corpuscles in severe anæmias. Herz, Daland, and Friedheim found it by centrifugalising and by enumeration. Biernacki (15) found it by sedimentation; and I have confirmed it by the same method in two cases of most severe anæmia (1 million red corpuscles per c.mm.). The red corpuscles seem to be enormously increased; in my cases the value was as much as 1160 C., instead of 500—600 C. If this proves to be true, some relation between the volume of, and the increased amount of salt in the corpuscles observed by Biernacki and myself may be deduced.

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6. THE HÆMOGLOBIN AND THE GASES OF THE BLOOD.

The red colour of the blood is due to a compound of iron with an albuminous body, hæmoglobin (hæmoglobulin, hæmocrystallin), which contains albumen 96 per cent., and hæmochromogen 4 per cent. As the red corpuscles in all probability have no cell membrane, the hæmoglobin cannot be simply enclosed, but is probably fixed in the stroma. Some facts, *e.g.* the relation of the corpuscles to salt solutions, seem to indicate that the hæmoglobin is not held in a simple mechanical manner by the stroma, but that the fixation may be due to some chemical combination (Hoppe-Seyler, 1). In the circulation we have its combination with oxygen, oxyhæmoglobin, and the so-called reduced or plain hæmoglobin. It crystallises in certain conditions in its different combinations, sometimes even in the living body. The crystals of human oxyhæmoglobin are rhombic plates of a yellowish-red colour, but so far have not been produced in sufficient quantities to admit of analysis. This, however, has been done in other animals. The hæmoglobin in these differs in some respects from human hæmoglobin; but beyond this the analyses do not show a satisfactory conformity. The following table from Kossel (2) gives the results of different observers.

TABLE.

Animal.	C	H	N	O	S	Fe	P	Analyser.
Horse	54·87	6·97	17·31	19·73	0·65	0·47	—	Kossel, 'Zeitschr. f. phys. Chem.,' Bd. ii, p. 149.
,,	54·76	7·03	17·28	19·81	0·67	0·45	—	Otto Pflüger's 'Archiv,' Bd. xxxi, p. 240.
,,	54·40	7·20	17·61	19·67	0·65	0·47	—	Bücheler, 'Zeitschr. f. phys. Chem.,' Bd. viii, p. 362.
,,	54·80	7·00	17·06	19·86	0·68	0·47	—	Nencki and Sieber, 'Kölliker Gewebelehre.'
,,	51·15	6·76	17·94	23·42	0·3899	0·3351	—	Zinnoffsky, 'Zeitschr. f. phys. Chem.,' Bd. x, p. 60.
Dog	53·85	2·32	16·17	21·84	0·39	0·43	—	Hoppe-Seyler, 'Med.-chem. Unters.,' 1871, p. 189.
,,	54·57	7·22	16·38	20·93	0·568	0·336	—	Jaquet, 'Zeitschr. f. phys. Chem.,' Bd. xiv, p. 289.
Pig	54·71	7·38	17·43	19·60	0·479	0·399	—	Hüfner, 'Festschr. f. C. Ludwig,' 1887, p. 74.
Cow	54·66	7·25	17·70	19·54	0·437	0·40	—	
Goose	54·26	7·10	16·21	20·69	0·59	0·43	0·34	Hoppe-Seyler, l. c.
Hen	52·47	7·19	16·45	22·50	0·859	0·335	0·197	Jaquet, l. c.

Certain of the differences may be due to the technical difficulties of the analysis; but the question of the existence of different hæmoglobins in the blood of the same animal has often been considered, more especially by Bohr (3), who observed that specimens of hæmoglobin from the same blood under exactly the same external conditions could combine with different amounts of oxygen, and that different crystals from the same blood might have a varying constitution. Hüfner contested this; he showed on the one hand that Bohr's experiments were not free from error, and on the other, by means of spectro-photometric estimations in the blood of cattle, that the absorptive power of the hæmoglobin was uniform for both oxygen and carbonic dioxide. The spectroscopic relation of hæmoglobin and oxyhæmoglobin is the same for the blood of all warm-blooded animals, the former showing a broad absorption-band between the lines D and E in addition to some darkening at each end of the spectrum. This can be changed into that of hæmatin by the addition of dilute acid or alkali. Oxyhæmoglobin shows a darkening in the blue and violet, and two absorption-bands in the yellow and green between D and E, the one near the red being narrower and darker, the one in the green broader and less defined. We are at present almost entirely ignorant of the place and manner of the origin and destruction of the hæmoglobin in the animal organism.

A. Swartz (5) maintains that the formation and destruction of hæmoglobin is a common property of animal protoplasm, professing to have observed that splenic pulp cells rapidly break up crystalline hæmoglobin, and after a time build it up again. These observations have been shown (Gürber, 6) to be erroneous.

The biological *rôle* of hæmoglobin lies in its character of oxygen-carrier of the organism. The oxygen in it is loosely combined. According to Hüfner (7), 1 g. of hæmoglobin can combine with 1·16 c.c. of oxygen; according to Preyer (8) the amount is 1·27 c.c. (at 0° C. and 1000 mm. pressure). It is usually estimated that 100 g. of human blood contains about 14 g. of hæmoglobin under normal physiological conditions.

The hæmoglobin obviously has a great influence on the amount of oxidation in the body. We have an enormous literature at our disposal concerning the amount in different conditions, a fact which is due to the introduction of a number of simple instruments. These instruments are, unfortunately, however, as unreliable as they are simple, except between wide limits. Our knowledge of the total respiratory surface is based on the hæmatocrit, and is still more unsatisfactory. Before this latter instrument was invented attempts were made to form some idea of the distribution of the hæmoglobin in the blood by estimating its amount and counting the red corpuscles. Any inferences made in this way depended on the question whether the amount of hæmoglobin in the individual cells is constant in different people under conditions of both health and disease. This question, first discussed by Hayem, was soon answered in the negative. If H be the amount of hæmoglobin in a specimen of blood, N the number of red corpuscles, and W the hæmoglobin value of a cell, then $W = \frac{H}{N}$. In normal cases H and N are each 100 per cent. of normal, *i.e.* under ordinary conditions $W = 1$. In pathological conditions W may be $>$ or $<$ 1. Variations of this kind, and the variations in the amount of hæmoglobin in the circulation in health and disease, are discussed in the clinical part of this book. I must, however, mention certain general points about the hæmoglobin index, W. It is stated to this day that $W < 1$ is a sign of chlorosis, and $W > 1$ is a sign of pernicious anæmia. From innumerable observations of my own and others, I have no hesitation in saying that the hæmoglobin index does not afford the slightest indication of the nature of any particular pathological change in the blood. We may say that in the different forms of anæmia $W = 1$ only when the red corpuscles and hæmoglobin are medium in amount, that $W < 1$ where there is an increased number of corpuscles, and that $W > 1$ when the number of red corpuscles is small. The reason for this is unknown. It has been suggested that $W > 1$ in pernicious anæmia owing to the increased volume which has been noticed in the individual cells; but we must remember that in these cases we get microcytes as well as macrocytes. The modern opinion is that the average amount of hæmoglobin in the red corpuscles is not constant in different diseases. It remains to be proved whether the inconstancy is as great as the instruments in use indicate. The incongruity of the values found by estimating the iron (Biernacki [10]), and the demonstrated unreliability (Dehio [11]) of the hæmometers for low numbers, suggest that the instrument may have something to do with it; at any rate, no deduction as to the number of red corpuscles can be made from estimations of the amount of hæmoglobin and *vice versâ*.

Hæmoglobin forms another and more stable compound with oxygen, namely, *methæmoglobin* (Hüfner and Külz [12]). Blood which contains this body is brownish red or brownish black. In dilute acid or neutral solution methæmoglobin shows spectroscopically four absorption-bands. The most characteristic is on the boundary between the red and orange, between C and D. On the right is a narrower band near D, a broader near E, and finally a similar one between E and F. Dittrich (13) found only the first two bands. On careful addition of ammonium sulphide the spectrum changes into that of oxyhæmoglobin and reduced hæmoglobin. It is consequently distinguished from the spectrum of acid hæmatin, which on the addition of ammonium sulphide changes into that of reduced hæmatin.

Methæmoglobin appears in the blood especially after poisoning with certain substances, the so-called blood poisons. Tschirkoff (14) claims to have found it in the bloood of Addison's disease. De Ruyter (15) has observed a similar, if not identical, substance in a case of malignant œdema.

The so-called blood poisons.—In general this heading includes those substances which, by chemical or morphological action, render the blood unfit for its respiratory duties. These are, however, so abundant, that it is now customary to include only those bodies which by direct action render the oxyhæmoglobin useless from a respiratory point of view. The methæmoglobin-forming poisons are the most important from a practical standpoint. Carbonic monoxide poisoning is also important; but the formation of compounds between hæmoglobin and nitrous oxide, sulphuretted hydrogen, cyanogen, etc., is less often met with. Amongst the methæmoglobin-forming substances are the chlorates (references 17—24), hydroxylamin (references 25—29), amyl nitrate (30—32), phenyl-hydrazin (33), acetyl-phenyl-hydrazin, pyrodin (34—37), aniline (38), nitro-benzol (39, 40), kairin, thallin, hydrochinon, iodine, bromine, turpentine, ether, osmic acid, pot. permang., sod. nitrate, pyrocatechin, pot. ferricyan. (41), phenacetin (42), antifebrin (43, 44, 45), the poison of certain fungi (*Helvella esculenta* [46]), the so-called saponines (47), and certain snake poisons (48). These can be separated, inasmuch as some, *e. g.* the chlorates, first convert the hæmoglobin, and then break up the altered corpuscles; whilst others, *e. g.* arseniuretted hydrogen and the fungus poison, are said to break up the corpuscles first, and then convert the hæmoglobin. I have convinced myself, however, that the arseniuretted hydrogen also converts the hæmoglobin first. As these different poisons seem to act in an analogous manner as far as their toxic action is concerned, I will only discuss one which is of practical importance, viz. the chlorates. Marchand was the first to study the poisonous action of these salts experimentally in dogs. He stated that in acute poisoning by chlorates, death was due to the formation of methæmoglobin. Stokvis controverted him, saying that experiments on rabbits showed that death was due to the direct action of the salts, and that the methæmoglobin had merely the significance of a post-mortem appearance. Cahn thought that these differences of opinion might be due to the difference in the animals used. He tried to reconcile them by causing alterations in the blood of rabbits, so as to make it more similar to that of dogs, and then poisoning them with chlorates. He was, however, unsuccessful. Leuhartz and Riess proved that the methæmoglobin could be demonstrated during life in the blood-vessels of the animals. My experiments show that in dogs death from chlorates is due, at any rate in great part, to asphyxia, brought about by want of hæmoglobin capable of carrying on respiration. The direct poisonous action of the salts is in dogs quite subordinate. In man, probably, the action is similar to that in dogs, for outside the body human blood resembles dog's blood far more closely than rabbit's blood, especially as regards the resistance of its corpuscles and hæmoglobin. In herbivora the relations are different. In rabbits it is certain that death occurs without the characteristic change in hæmoglobin. In fact, we must wait at least one and a half hours after death before we can demonstrate the presence of methæmoglobin. In these cases, therefore, death is directly due to the poisonous action of the salts. The question whether the poison causes death partly by destruction of the red corpuscles must be answered in the negative, for even when the change in hæmoglobin occurs, there is no diminution in the number of the corpuscles. The chlorates act on intravascular blood just as they do on blood outside the body, namely, as a hæmoglobin poison, and only secondarily cause the exit of hæmoglobin from the cells. But the destruction of the red corpuscles is not only due to the change of hæmoglobin, for other substances (*e. g.* amyl nitrate) cause the formation of methæmoglobin without any destruction of the corpuscles. Hence the presence of the salts in the plasma must play some part.

In acute cases of chlorate poisoning, then, in carnivora and man, death is caused by asphyxia, due to deficiency of hæmoglobin which is capable of carrying on respiration (for methæmoglobin in itself is not poisonous), the saline action of the chlorates playing a subordinate part; whereas in herbivora the latter factor is the more important. When we come to subacute or chronic cases the relations are much more complicated. Here the causes of death are to be sought not only in saline action, in destruction of corpuscles, and in formation of methæmoglobin, but in formation of thrombi (Silbermann [49]) and, most important of all, in irritation of the kidneys. All authors agree that animals so poisoned die through the production of nephritis. Stokvis thinks that this is due to the irritation produced by the excretion of the salts; whereas Marchand believes it to be secondary to the alterations in the blood. I agree with Marchand, and think that it is due to the breaking up of the red corpuscles. My experiments show that this breaking up occurs after the lapse of a sufficiently long time, even when the amount of chlorates in the blood is small. Clinical observations lead to the same conclusion (Brandenburg [50]).

Carbon monoxide poisoning differs from the methæmoglobin-forming poisons in the peculiarity of the change in hæmoglobin. If oxyhæmoglobin is brought into contact with gases containing carbon monoxide (charcoal fumes, coal gas), carbon-hæmoglobin is formed without any dissolution of the red corpuscles, so that the hæmoglobin is withdrawn from respiration. Blood so changed is marked by its bluish-red colour, and shows spectroscopically two bands further to the right than the oxyhæmoglobin bands. These bands are unaltered by the addition of ammonium sulphide. If any animal breathes air containing carbon monoxide, a portion of the hæmoglobin is changed in this manner. The amount of conversion varies according to Gréhaut 51); cf. J. Bock, 52) with the amount of carbon monoxide in the air, and follows Dalton's law.

Gréhaut obtained the following results:

TABLE.

CO contained in respired air .	$\frac{1}{1000}$	$\frac{1}{2500}$	$\frac{1}{5000}$	$\frac{1}{7500}$	$\frac{1}{10000}$
In 100 cm.^{3} blood CO cm.^{3} .	9·5	6	4·9	2·8	1·2

Air CO.	Gases of the blood.			
%	CO_2 per cent.	O_2 per cent.	N per cent.	CO per cent.
1·0	28·9	12·2	1·5	5·5
0·5	51·8	15·5	1·5	2·8
0·33	42·2	13·4	1·8	1·7
0·25	40·4	21·5	1·5	1·3

Low percentages of carbon monoxide are easily borne by animals and men. Grüber (53) came to the conclusion that ·4 per cent. was the toxic limit in air. Fodor (54), Biefel, and Polek (55) placed it somewhat lower, between ·3 and ·4 per cent. This gives, according to the above law, the toxic amount of carbon monoxide in blood as about 20 per cent. The old views with regard to the mechanism of acute carbon monoxide poisoning were, that death was entirely due to asphyxia from the deficiency in respiratory hæmoglobin (Hoppe-Seyler [56]). Lately Geppert (57) and Marcacci (58) have shown that the carbon monoxide probably has in addition a specific toxic action on the central nervous system and the nervous apparatus of the heart. The relations in subacute and chronic cases are of course not so simple, as complications of the greatest variety may endanger life (bronchitis, pneumonia, neuritis, etc.). With regard to the spontaneous process of cure after carbon monoxide poisoning, it used to be thought (Kreis, 59) that oxidation of carbon monoxide to carbon dioxide took place, but Eulenberg (60) and Gaglio (61) have shown this to be erroneous, so that now it is generally held that the carbon monoxide is gradually got rid of through the lungs. The loss of carbon monoxide which a mixture of oxygen blood and carbon monoxide blood undergoes on exposure to air is, as a matter of fact, small compared with its loss of oxygen. On this point Saint-Martin (62) published the following experimental result :

TABLE.

	Original amount in the blood.	After 9 hours.	After 18 hours.	After 36 hours.
CO_2	35·11 %	37·05 %	51·79 %	62·5 %
O_2	13·89 ,,	9·24 ,,	4·9 ,,	0·38 ,,
CO	2·54 ,,	1·4 ,,	1·25 ,,	1·15 ,,
N_2	2·25 ,,	2·25 ,,	2·05 ,,	2·3 ,,

This shows, what indeed has long been known, that outside the body carbon dioxide is formed at the expense of the oxygen in the blood, but also that it is present in comparatively small amounts in carbon monoxide blood. The carbon dioxide formation in normal blood is estimated at 3—4 per cent. per hour. In this experiment it was only about ·5 per cent. The amount of carbon monoxide altered in the first hour only, and then remained approximately constant. This circumstance is clinically and medico-legally of great importance. In cases of recovery from carbon monoxide poison, carbon monoxide can be demonstrated in the blood for some days. Blood taken from corpses, shut off from air in the earth, shows the presence of carbon monoxide much longer than blood allowed to putrefy outside the body. Piotrovsky (63) gives the following experiments—dog's blood treated with carbon monoxide and allowed to undergo putrefaction in the air :

TABLE.

On Jan.	12th	24·7 % CO.
„	20th	23·5 „ „
„	28th	22·2 „ „
On Feb.	8th	20·3 „ „
„	16th	15·5 „ „
„	26th	10·2 „ „
On Mar.	3rd	6·3 „ „
„	14th	4·6 „ „
„	22nd	1·8 „ „

Another dog, buried on 12th January, was exhumed on March 28th. The blood still contained 11·7 per cent. carbon monoxide.

It was stated above that the hæmoglobin in the arterial system is for the most part oxy-hæmoglobin. In addition to oxygen, the blood contains and gives up, on diminution of pressure, *carbon dioxide and nitrogen.* The oxygen is not simply dissolved in the blood, but is in a state of loose chemical combination with the hæmoglobin. Ozone is never present in the blood. The amount in oxygen of arterial blood is always higher than that in venous blood, but even in arterial blood the maximum amount of oxygen that can be taken up is not reached. Meyer and Biarnes (64) designate the actual amount of oxygen in the blood as O_1, and the amount after shaking up with oxygen as O. Then on the one hand O represents the respiratory capacity of the blood, and on the other $\frac{O_1}{O}$ is a co-efficient giving the amount of saturation. If $O_1 = O$ the co-efficient would be 1, and the greater the deficiency of respiratory hæmoglobin the nearer would the co-efficient approach 1. So Meyer and Bairnes found in a normal dog $\frac{O_1}{O} = \frac{19}{25} = \cdot 76$.

After bloodletting $\frac{O_1}{O} = \frac{17\cdot 5}{20\cdot 5} = \cdot 85$.

Before slight carbonic monoxide poisoning $\left.\right\}$ $\frac{O_1}{O} = \frac{18}{24} = \cdot 75$;

and after ,, $\frac{O_1}{O} = \frac{13\cdot 2}{14\cdot 7} = \cdot 9$;

whilst I obtained the following result in a dog poisoned with potassium chlorate (65):

$$\frac{O_1}{O} = \frac{7\cdot 6}{7\cdot 8} = \cdot 97.$$

We see, then, that when the needs of the body demand it, the hæmoglobin, which otherwise escapes, undergoes oxidation. Amongst the physiological influences which affect the amount of oxygen (O_1) we must mention loss of oxygen from the air and increased temperature (Zuntz, 66), both of which are said to cause diminution of oxygen in the blood. On the latter point Worm-Müller and Bert's (67) experiments are, I believe, so far uncontested. On the former point, Viault (68) has lately shown that compensatory processes probably come into play. He noticed that polycythæmia occurred in high altitudes, and so was led to estimate the amount of oxygen in animals in these regions. He found the amount of oxygen to be the same as it was in animals on the plains in spite of the diminished pressure and the polycythæmia. Other causes of variation in amount of oxygen, apart from oligocythæmia, are to be sought in obstruction of the respiratory apparatus from nervous or mechanical reasons.

The relations of the carbon dioxide in the blood will be discussed in the section on alkalinity. The nitrogen exists in simple solution, and not in chemical combination; its amount is therefore proportional to the atmospheric pressure, so that it rapidly disappears when air devoid of nitrogen is inspired (Pflüger, 70). Arterial and venous blood both contain about 2 per cent. volume of nitrogen at medium atmospheric pressure. There is apparently no biological significance in the variations in the amount of this gas in the blood. Gréhant (71) claims to have found small amounts of marsh gas even in fresh normal blood.

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VII. The Alkalinity of the Blood and Serum.

Blood freshly taken from a warm-blooded animal has a slightly alkaline reaction to litmus. Salkowski (1) and Cantani (2) observed an acid reaction just before death in rabbits; the former after sulphuric acid poisoning, the latter in cholera. The alkalinity of blood, though long known, first assumed significance when it was shown by Walter to be an elementary condition of the continuance of life. He poisoned rabbits with hydrochloric acid, and found the amount of carbon dioxide that could be pumped out of the blood was much diminished. This he explained as follows: —The acid is absorbed, and forms salts with some of the alkalies in the blood, which are passed in the urine; there is consequently a deficiency of alkali, and a sufficient amount is not left to combine with the carbon monoxide formed by metabolism. This theory has found general acceptance in the case of herbivora. In carnivora (and man) it is not absolutely true, for it appears that it is not the alkali of the blood, but the ammonia, which in the first instance neutralises the acid. Certain pathological considerations render Walter's observation important. Thus there are conditions in which the excretion of ammonia is increased, and Pflüger (4) has found that the blood of dogs with suppurating wounds contains less carbonic dioxide than normal blood.

The power of blood to combine with acids conveys two different ideas, according as we look at it from a biological or chemical point of view. Biologically it means the quantity of carbon dioxide with which the blood can combine in virtue of its power to combine with acids. Chemically it is identical with the degree of alkalinity. Whether this point has a biological importance we do not know. Two methods have been used to determine it; the analytical method, *i. e.* the estimation of carbon dioxide after the addition of an acid, and the alkalimetric method. These were considered to be comparable, since it was said that the carbonates, the only carbon dioxide carriers, formed far and away the greatest part of the alkalies in blood. But Bohr (5) and Torup (6) showed that probably some carbon dioxide was simply dissolved, and that it was combined not only with the alkalies, but also, though loosely, with the albumins, more especially hæmoglobin and globulin. This view was not much credited; in fact, Jacquet (7) maintained that Zuntz's (1) method and the analytical method produced proportional values, so that the alkalimetric method could be used in place of, and even preferably to, the estimation of carbon dioxide. Löwy (8), however, has shown that Jacquet's and all alkalimetric methods give erroneous results, and that the true alkalinity is much greater than Zuntz's or similar methods would lead us to suppose. We must therefore not compare results obtained by the two methods, but consider them separately as estimations of two different things.

The amount of carbon dioxide that can be pumped out of a specimen of blood after the addition of an acid depends on the amount of carbonates it contains, and also on the carbon dioxide otherwise present in the blood. The degree of alkalinity, on the other hand, depends, according to the method used, on the power the alkalies (Na_2HPO_4, Na_2CO_3), the unsaturated salts ($NaHCO_3$), the albumins, and the substances formed by the addition of acid have to combine with acids, and is estimated by the amount of salts present which can thus combine with the acids.

The variations of the carbon dioxide in healthy blood are considerable ; they depend, apart from other influences, on the quality of the blood investigated.

Venous blood always contains more carbon dioxide than arterial. Schäffer (10) found 39·5 and 45·3 per cent. ; Setschenow (11) gave the average amount of arterial blood as 40·3 per cent. ; Kraus (12) found in venous blood a strikingly small amount, viz. only 33·37 volumes per cent. Many physiological influences affect the amount of carbon dioxide. Amongst these are the temperature and muscular exercise. The first lessens, the latter increases the amount (Mathieu and Urbain, 13 ; Witkowski, 14).

Pathological variations are often observed. The observation of Pflüger, mentioned above, of diminution of the amount of carbon dioxide in dogs with suppurating wounds, caused many observers (references 15—20) to study this question. They all found a diminution of carbon dioxide in the blood in febrile conditions. According to Geppert (15) the loss in the amount of carbon dioxide is approximately proportional to the rise of temperature, and is due to a change in the metabolism which produces an excess of acid. Minkowski (21) got similar results. He asserted that he had found lactic acid in the blood in some of his cases. Nencki and Sieber (22), however, have raised objections to his methods. Lehmann's (20) discovery that lactic acid undergoes combustion in the body, and forms carbonic dioxide, does not negative this statement. Again, other experiments, including those of Kraus, supported the view that in fever there was excess of acid in the blood. Kraus made positive observations on the diminution of carbonic dioxide in the venous blood of human beings with fever, and also noticed that the power of combining with bases was increased. As certain unsaturated salts ($NaHCO_3$, NaH_2PO_4) present in the blood give an acid reaction with certain pigments—*e. g.* phenol-pthaleïn, in spite of its alkaline reaction to litmus—the blood must have the power of combining with bases. In this way the power of the blood to combine with bases (Kraus) is due to an increase of the unsaturated acid salts. Kraus found in cases with a high temperature that the carbonic dioxide was 10—20 volumes per cent. as against about 30 per cent. under normal conditions. The capacity to combine with bases, which was normally ·199, increased in these cases to ·23, ·209, and ·237.

It is consequently true that, as in Walter's acid-poisoning experiments in rabbits, there is in the case of man a diminution of carbon dioxide, and an increase of acid metabolic products in the blood during fever. The cause of this is not yet certain. The temperature itself does not sufficiently explain it, for Geppert and Kraus have shown that the diminution of carbon dioxide outlasts the period of increased temperature. It is generally held that tissue destruction, with insufficient oxidation of the products, causes the formation of intermediate acid (subacid) substances, and that the above phenomena are due to this cause. Kraus thought that the destruction of red corpuscles was also a cause, but against this we have the fact that these corpuscles contain a considerable amount of alkali.

We have estimations of carbon dioxide in other conditions. In cancer Klemperer found 14·8 to 18 per cent. in four cases, whilst I obtained in five cases values varying from 19·8 to 20·5 per cent., so that the carbon dioxide is much diminished. The cause of the diminution here is as uncertain as it is in fevers, but it may also be due to similar tissue destruction. In diabetic coma older work had shown the probability of acid poisoning from the formation of oxybutyric and diacet-acetic acids (references 24—27). Minkowski notes a case in which the amount of carbon dioxide in arterial blood was 4·39 per cent., and Kraus had cases in which the amounts in venous blood were 12·44 and 9·83 volumes per cent. In the last case the acidity, *i. e.* the capacity to combine with bases, had risen to ·347 per cent. NaOH. All these data point to the existence of acid poisoning in the coma of diabetes. Kraus himself has published an exception where the amount of carbon dioxide was normal, but this has received no consideration. In leukæmia Kraus found 20·29 per cent. of carbon dioxide, *i. e.* some diminution.

The result of analytical investigations shows, then, that in fevers, cancer, and diabetic coma a diminution of carbon dioxide occurs in the blood; further, it is probable from analogy with Walter's experiments, and still more on account of the demonstration of the increased capacity of the blood to combine with basic substances, that in these cases we have a condition of acid poisoning.

The results of alkalimetric observations ought to be prefaced by a criticism of the methods used. We may say in general with Löwy (28) that they never give the total alkalinity of the blood, but merely the amount of alkali in an unknown amount of serum or plasma taken from the specimen to be examined. Again, even this is not accurately done, for a certain amount of alkali gets into the plasma from the corpuscles (Limbeck and Steindler, 29). These methods, so full of error, have unfortunately been almost exclusively used hitherto. The results, being more than doubtful, will be mentioned as briefly as possible. The normal values are ·26—·3 (30, 31). Men (32) have more alkali than women. Daily variations (33) of considerable degree are said to occur. It is universally agreed that the degree of alkalinity is diminished in fever (34), in cancer, anæmia, leukæmia, uræmia, cirrhosis of liver, and osteomalacia.

We must compare these values with those found in an examination of the whole blood (as opposed to the plasma). Löwy found an average of 447·68—508·96 mg. NaOH per 100 c.c. blood. Contrary to expectations, he found in a few cases, not only no decrease, but even some increase in the alkalinity of the blood, in which a diminution was considered to be an established fact.

Löwy gives the following results:

TABLE.

	Mgrs. NaOH for 100 cm.^{3} blood.
In diabetes mell.	886·7, 964·0, 615·5, and 593·9
,, nephritis parench.	936·6, 1008·0, 595·2.
,, chronic	980·16, 987·2, 982·6, 683·2
,, sepsis puerperalis	990·6
,, sept. endocarditis	885, 1008·3, 1011·2
,, anæmia	675·2, 555·2
,, pneumonia	384
,, acute gout	590·4
,, rheum. art. acute	467·2
,, chlorosis	662·3, 541·8
,, pneumonia	827·68, 486·4

Schultz-Schultzenstein (36) used a similar method, and obtained an average in normal cases of ·62 per cent. NaOH. Steindler and I (29) investigated sixty-two cases. In one set we titrated serum, obtained by centrifugalisation or spontaneous coagulation, with litmus and $\frac{1}{10}$ hydrochloric acid. Tables I and II give the results. In the others the alkalinity of the serum spontaneously expressed, and that obtained by centrifugalisation, were compared, after coagulation had occurred according to my method. These are given in Tables III and IV.

TABLE I.

Obtained by centrifugalising defibrinated blood.

No.	Diagnosis.	Alkalescence, Vol. per cent. NaOH.	Remarks.
1	Healthy	0·256	Temperature normal.
2	,,	0·224	
3	Hip disease	0·380	
4	Emphys. plm.	0·256	
5	,,	0·332	
6	,,	0·268	
7	Osteomalacia	0·260	
8	,,	0·216	
9	Anæmia	0·184	
10	Tetanus	0·220	
11	After influenza	0·300	
12	Tub. miliaris	0·200	High fever.
13	Influenza	0·248	
14	Rheum. acute	0·232	
15	Pneumonia	0·256	
16	Neph. chron. pneumonia	0·204	

TABLE II.

Obtained by spontaneous coagulation of the blood.

No.	Diagnosis.	Alkalescence, Vol. per cent. NaOH.	Remarks.
17	Neuritis	0·280	Temperature normal.
18	Hemiplegia	0·296	
19	Nephr. chron.	0·259	
20	After influenza	0·372	
21	Emph. plm.	0·336	
22	Sine morbo	0·296	
23	Nephr. chron.	0·224	
24	Pneumonia	0·300	High fever.
25	Bronchitis	0·332	
26	Pneumonia	0·224	
27	Tub. miliaris	0·232	
28	Pleuritis	0·296	
29	Morbilli	0·224	
30	Typh. abd.	0·226	
31	Influenza	0·284	
32	,,	0·268	

Table III.

In healthy and afebrile conditions.

Diagnosis.	Degree of Alkalescence of defibrinated blood. Vol. per cent. NaOH.	Degree of alkalescence of the serum. Vol. per cent.	
		of the defibrinated blood. NaOH.	of the spontaneously coagulated blood. NaOH.
Healthy	0·230	—	0·188
,,	0·220	0·140	0·192
Hysteria	—	—	0·176
Bronchitis	0·296	0·190	0·200
,,	0·228	—	0·184
,,	0·280	0·170	0·200
Hip disease	0·336	0·160	0·200
Nephr. chron.	0·340	0·180	0·190
,,	0·246	—	0·206
Emphys. plm.	0·200	0·168	0·184
,, ,,	0·230	0·184	0·204
,, + nephr. chron.	0·228	0·100	0·120
Chlorosis	0·208	0·145	0·192
Tub. plm.	0·336	—	0·197
CO poisoning	0·268	0·112	0·160
Nephr. chron.	0·384	—	0·144
Carcin. recti	0·281	0·160	0·216
Alcoh. acutus	0·304	0·156	0·194
Intox. c. acid. muriat.	0·308	—	0·152

Table IV.

Fevers.

Diagnosis.	Temperature.	Amount of alkalescence of blood in Vol. per cent. NaOH.	Alkalescence of the serum in Vol. per cent. NaOH.	
			of the defibrinated blood.	of the spontaneously coagulated blood.
Pneumonia	39·5	0·304	0·176	0·178
,,	37·8	0·180	—	0·164
,,	39·8	0·220	—	0·173
,,	39·7	0·179	—	0·179
,,	39·8	0·200	—	—
,,	40	0·260	—	0·180
,,	39·4	0·291	—	0·197
Pleuritis	39	0·268	0·158	0·188
,,	37·8	0·324	—	—
Meningitis	39·8	—	—	0·179
Malaria	40·4 Riger	0·200	—	0·164

We see from Tables I and II that—

1. The values in II average higher than those in I, *i. e.* that the serum obtained by spontaneous coagulation can combine with more acid than that obtained by centrifugalisation of arterialised blood.
2. Considerable differences occur in health.
3. The variations are practically the same as in health.

Tables III and IV give similar results. They show also—

4. That the alkalinity of the whole blood is always higher than that of the serum ; and
5. In the majority of cases associated with high temperature the values are normal or increased, although low values are sometimes found.

It is obvious, in view of these cases and those of Löwy's, that *diminished alkalinity of the blood or serum does not occur regularly in febrile conditions.* It must be noticed that this does not affect the theory (discussed above) of acid-poisoning in fever.

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VIII. The Osmotic Relations of the Blood.

Every cell, according to the substance dissolved in it, has certain osmotic powers, and if no exchange is going on between it and the fluid around it the two must be in osmotic equilibrium. The sum of these powers is called *Turgor,* and De Vries was the first to estimate it in plant cells. His method was to find the concentrations of different salt solutions which had the same "Turgor" as the cells. He gave the name *Isotonic* to such a solution. De Vries found the two following laws:—(1) The isotonic concentration of a particular salt depends on its molecular volume, and (2) the isotonic value of a salt is the sum of the values of the base and of the acid.

The idea of applying this to animal cells, especially red corpuscles, first occurred to Donders, whose pupil Hamburger (1) pursued the subject in a long series of investigations. A new field of observation was thereby opened to physiologists and pathologists. Hamburger's results may be summarised as follows:—If a drop of blood is allowed to fall into water, the corpuscles undergo dissolution, and the blood becomes laky ; this result does not occur, however, if a saline solution of a certain concentration be substituted for the water. A concentration can be found for every specimen of blood and for every different salt, which is just sufficient to prevent the egress of the hæmoglobin from the corpuscles. This solution is isotonic with the corpuscles, and represents its amount of "tone." It gives us also a measurement of its resistance to the dissolving action of water. In Hamburger's work it is implicitly assumed that the hæmoglobin is simply suspended in the corpuscles, and that the latter have a cell membrane. He found, and I have (2) corroborated him, that the isotonic concentration of a salt varied with its molecular weight. A constant can be found for each specimen of blood, which, multiplied by the molecular weight of a salt, gives the isotonic concentration of the latter.

TABLE.

	Constant.	NaCl Mol. wt. 58.		$NaNO_3$ Mol. wt. 85.		$NaClO_3$ Mol. wt. 106·5.	
		Experiment.	Calculation.	Experiment.	Calculation.	Experiment.	Calculation.
Rabbit.	$\frac{0·88}{100}$	0·55	0·51	0·75	0·75	0·85	0·93
Man .	$\frac{0·765}{100}$	0·45	0·45	0·70	0·65	0·75	0·81
Dog .	$\frac{0·756}{100}$	0·45	0·45	0·70	0·64	0·70	0·80

This is, however, true only in the case of monobasic salts. In the following table rabbit's blood was used, and the isotonic concentration found by experiment compared with that found by multiplying the molecular weight by $\frac{\cdot 88}{100}$:

TABLE.

	Salt.	Formula.	Molecular weight.	Isotonic values.	
				Experiment %.	Calculation %.
Monobasic	Chloride .	$ClNa$	58·5	0·55	0·51
	Bromide .	$NaBr$	103	0·9	0·91
	Iodide .	NaI	150	1·40	1·32
	Nitrate .	$NaNO_3$	85	0·75	0·75
	Chlorate .	$NaClO_3$	106·5	0·85	0·93
	Acetate .	$NaC_2H_3O_2$	82	0·70	0·72
Polybasic	Sulphate .	Na_2SO_4	142	0·80	1·25
	Phosphate	Na_2HPO_4	142	0·95	1·25
	Tartrate .	$Na_2C_4H_4O_6$	194	2·0	1·71
	Chromate .	Na_2CrO_4	162·5	0·70	1·37
	Citrate .	$Na_3C_6H_5O_7$	258	1·30	2·27

The isotonic concentration depends, of course, as much on the blood used as on the salt. The first table shows that it is different for different animals, and further, that in the same animal it is higher for venous than for arterial blood. If we take blood and pass carbon monoxide through it, the isotonic concentration increases. Human blood shaken with air shows an isotonic concentration of ·46—·5 per cent. sodium chloride; carbonic dioxide increases this to ·56 and upwards. Carbon monoxide and arseniuretted hydrogen also increase the isotonic co-efficient. A trace of acid causes an increase, a trace of alkali a diminution. We can also cause variations by passing gases through the blood, or by adding acid and alkali alternately. I found the isotonic concentration of a specimen of horse's blood to be ·52; on the addition of carbonic acid gas this became ·64, but when air was passed through the blood it sank back to ·54 per cent. sodium chloride. It is obvious that the plasma must have at least the same isotonic value as the corpuscles, for otherwise the contents of the corpuscles would pass into the plasma until osmotic equilibrium was restored. It is not, however, sufficient for the plasma to have only the same isotonic co-efficient, for a minimum of water would, on passing into the circulation from the tissues, immediately have a deleterious action on the corpuscles; the osmotic elasticity of the plasma therefore must be greater than the isotonic concentration of the corpuscles. Hence plasma and serum are always hypertonic.

Hamburger considers that these osmotic processes are purely physical phenomena. But various considerations appear to me to show that the subject is much more complicated. In the first place, the fact that red corpuscles remain intact in serum outside the body for hours or even days indicates that they are in osmotic equilibrium. In the course of time the corpuscles begin to undergo dissolution, and therefore the physical processes must be combined with some chemical changes. Secondly, the osmotic relations of two salt solutions depend on their concentration and the condition of the partition between them. In the case of the blood we have a fluid with much albumen and little salt in the corpuscles, and a fluid with less, and quite different, albumens and much salt outside the corpuscles. Therefore (1) the albumens must affect the osmotic power, or (2) part of the chlorides in the serum do not enter into the osmotic action. The first view is supported by the fact that the isotonic concentration of a saline solution, so far as horse's blood is concerned, is higher than the percentage of sodium chloride in the serum. I found the isotonic value of the corpuscles to be ·56 per cent. sodium chloride, whereas the serum contained only ·46 per cent. sodium chloride. In favour of the second view we have the facts that the total amount of chlorides in human serum, reckoned as sodium chloride, is in excess of the isotonic concentration of the corpuscles, and that a certain amount of salt is necessary to hold the serum globulin in solution. I found, *e. g.*, the amount of salt in the corpuscles to be ·2 per cent., the isotonic value of the corpuscles to be ·4 per cent., and the salts of the serum to be ·62 per cent., all reckoned as sodium chloride.

In any case we see that chemical action of some kind is a factor in this action, and this is corroborated by a fact noticed by Hamburger himself, viz. the isotonic value of the corpuscles remains constant when its medium is rendered more and more hypertonic.

In this connection Hoppe-Seyler's suggestion of a combination between the hæmoglobin and the stroma of the corpuscles is of interest.

Again, the fact that under the influence of carbon dioxide the corpuscles do not take up substances from the serum in the same proportion as they are contained in the latter, suggests that the red corpuscles have the power of selective imbibition, a view which excludes the action of a mere physical membrane. It seems likely that it is the connection of the hæmoglobin with the stroma that is altered, and not changes in a hypothetical membrane of the corpuscles.

Our knowledge of the theory of the variations in the isotonic value of the corpuscles is, as we see, quite rudimentary. Nevertheless its estimation is of practical interest, especially in so far as it gives us a measurement of the resistance of the corpuscles to distilled water. I (5) appear to have been the first to estimate the isotonic co-efficient in pathological cases. I found it to be about ·46 per cent. sodium chloride in health, whilst in diseases I obtained the following results:

TABLE.

	Disease.	Isotonic value in NaCl per cent.	Average.	No. of cases investigated.
Infection series	Pneumonia croup	0·46—0·58	0·5	6
	Typh. abdom.	0·42—0·54	0·49	6
	Erysipelas	0·44—0·58	0·5	5
	Meningitis tuberc.	0·42	0·42	1
	Influenza	0·42	0·42	2
	Abscess hepat.	0·46	0·46	1
General diseases	Diabetes mell.	0·44—0·5	0·46	3
	Osteomalacia	0·46	0·46	2
	Leukæmia lien.	0·52	0·52	1
	Purpura hæm.	0·43—0·56	0·5	4
	Catarrhal jaundice	0·38—0·42	0·39	15
	Jaundice from sepsis	0·38	0·38	1
Diseases of organs	Cirrhosis of the liver without jaundice	0·46	0·46	2
	Nephritis chron.	0·44—0·46	0·45	2
Anæmias	Anæmia gravis	0·52—0·54	0·53	2
	Chlorosis	0·38—0·4	0·39	2

This table shows the following results:

(1) *Acute infectious disease.*—Variations occur, but the values are often high especially in typhoid, erysipelas and pneumonia, *i. e.* the resistance to distilled water is diminished. The values may be normal or diminished; this may be dependent upon the stage of the disease.

(2) The conditions classed as those of *impaired nutrition.* The isotonic concentration seems to be constantly diminished in jaundice, whilst in leukæmia it is remarkably high.

(3) In *anæmia.*—The resistance, as might be expected, is diminished, but two cases of chlorosis showed an increased resistance.

Gallerani (6) found that the isotonic value was increased by starvation. Agostini (7) found that the resistance of the corpuscles was diminished in mental diseases, in neurasthenia, and in conditions of depression. Vicarelli (8) found that it increased during the last months of pregnancy, and continued to increase after confinement, reaching a maximum in the early stages of lactation. Cavazzani (9) mentions a slight decrease under the influence of injection or inunction of sublimate. Castellino (10) found increase of isotonic concentration in typhoid fever after the fifteenth day. Viola and Iona (11) obtained an increase directly after bloodletting; Bianchi and Mariotti (12) found it increased after the injection of different bacillary cultures, but that it diminished about forty-two hours after the injection of typhoid cultures.

Our knowledge is still more limited concerning the hypertonic co-efficient of the serum. Hamburger (13) found it to be constant after bloodletting, whilst I have found that the tone of the serum remained about constant whilst a dog was allowed to bleed to death.

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IX. Variations of the Blood in the Circulation.

Differences between arterial and venous blood.—The biological function of the blood as the nourishing fluid of the body necessitates changes during its circulation through the tissues. These can be divided into two groups according as they are due to individual organs, or to the general metabolism of the body. The former are little known, chiefly because the changes that occur while the blood circulates once through an organ are but slight. Arterial blood is light red, venous blood is dark. A part of the oxyhæmoglobin formed in the lungs is reduced by the carbon dioxide taken up from the tissues. Arterial blood contains more oxygen and less carbon dioxide than does venous blood. The amount of gaseous nitrogen is about the same in both venous and arterial blood. Schöffer (1) gives the following figures for dogs:—carotid blood 14—22 per cent. oxygen, 34—43 per cent. carbon dioxide, and 1·6—2·5 per cent. nitrogen; jugular blood 5—15 per cent. oxygen, 38—47 per cent. carbon dioxide, and 1·3—1·6 nitrogen. As far as is known the oxygen never disappears altogether; even in asphyxia 1 volume per cent. of oxygen was found (2), the carbon dioxide increasing at the same time; thus Ludwig (3) found the volume of carbon dioxide in asphyxiated dogs to be 54·2 per cent. Pathological disturbances of respiration cause a similar effect, the degree of which is proportional to the intensity of the disturbance. Consequently the oxygen is diminished in narcotised animals and the carbon dioxide increased. This is true both in artificial narcosis and in auto-intoxication; for example, I have found 50·35 per cent. carbon dioxide in the carotid blood of an uræmic dog (4). Other differences are said to exist in addition to these variations in the amount of gases. Malassez (5) stated that venous blood is richer than arterial blood in corpuscles. This was corroborated by some, and contested by others, until Cohnstein and Zuntz (6) showed that the differences observed resulted from small errors of observation, changes in the tone of the vessels, increase of blood-pressure in the veins, etc. According to these authors, the number of corpuscles in the blood, whether arterial or venous, is, as far as we can rely on our present methods, approximately the same. Manassein (7) formerly stated that the red corpuscles increased in size on contact with oxygen and decreased on contact with carbon dioxide. Later observations have shown exactly the converse (see below). The changes which the blood undergoes from respiratory interchange of gases and the metabolism of the tissues are of general interest, and still more so those that occur between the plasma and the corpuscles during a phase of the circulation. We owe the first observation on this subject to Hamburger (8), who has shown that the permeability of the red corpuscles alters under the influence of carbon dioxide and of oxygen, and that, therefore, an interchange occurs between the substances in the corpuscles and in the plasma, as soon as arterial blood is made venous or *vice versâ*. This interchange involves not only inorganic salts, but also certain organic material, such as sugar, albumen, and fat, and is found also to take place on the addition of dilute acids or alkalies. Carbon dioxide causes more especially an increase of the isotonic concentration of the corpuscles, and an increase of the dry residue of the serum, viz. alkali, phosphates, albumen, sugar, and fat. On the other hand the serum loses chlorides and water. The old relations are approximately restored if we pass oxygen through carbon dioxide blood, and it is probable that changes of this kind occur in the living body. The oxidation and reduction of the blood appears, then, to influence the distribution of the different components of plasma and of the corpuscles, and this circumstance must be of importance in the metabolism of the tissues. The actual facts, found by Hamburger, are incontestable, but the deductions he draws as to the interchange of matter, are logical only if we can show that the volume of plasma in the blood is not altered (9) under the influence of carbon dioxide. Now my experiments show that this assumption is untrue. Under the influence of carbon dioxide the corpuscles increase in volume by the selective imbibition of certain constituents of the plasma (water and chlorides), and in consequence of this the volume of the plasma diminishes—the old relations being approximately restored if oxygen gas is now added. The following table shows the results of my experiments :

TABLE..

	Portion I—Fresh defibrinated blood.	Portion II*a*—Defibrinated carbon dioxide passed through for ½ an hour.	Portion II*b*—Defibrinated carbon dioxide passed through for ¼ hour, then air for ¼ hour.
Volume of red corpuscles. .	683	934	637
N_2 in ,, ,, . .	28·6	35·8	32·3
ClNa in ,, ,, . .	1·7	2·8	1·4
Dry substance in red corpuscles .	224	264	234
Water ,, ,, .	526	743	472
Weight ,, ,, .	750	1007	706
Sp. weight ,, ,, .	1098	1078	1108
Isotonic concentration in red corp.	·52	·64	·54
Volume of serum ,, ,,	31·7 %	16·58%	41·84%
Total volume of the corpuscles .	68·27%	83·42%	58·16%
Chlorine of the serum . .	·45	·38	·44

I am able thus to concur with Hamburger's views that carbon dioxide causes—(1) an increase of the isotonic concentration of the corpuscles ; (2) a loss of water and chlorides of the serum. We see also that the corpuscles have absorbed nitrogen, chlorides, dry substances, and especially water. Hence the volume and weight of the corpuscles are increased, but the specific weight decreased. (3) The relations revert to the normal on the introduction of oxygen.

I also found similar but much smaller differences between arterial and venous blood.

Blood-corpuscles thus proceed, laden with oxygen, to the tissues, and give up oxygen; they then take up carbon dioxide and swell up, and finally return to the lungs where they resume their original size.

The increase of gland-cells during the process of secretion, and the diminution afterwards, is a well-known physiological process. We may compare the above swelling of the red corpuscles to this process, and if we call the lungs carbon dioxide-secreting glands, the red corpuscles will be in a position analogous to the gland-cells.

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X. THE PATHOLOGICAL RELATIONS OF COAGULATION.

Coagulation in the vessels may be caused by changes in the vessel walls—*e. g.* endocarditis, atheroma, aneurism. In these cases thrombosis is due to the adhesion of foreign substances to the vessel wall. But there are other cases where thrombosis occurs, in which it must be due to the presence of some active substance which causes coagulation—*e. g.* arteritis, phlebitis in typhoid, phlegmasia dolens. Such thromboses occur on injection of substances that dissolve or break up the corpuscles—*e. g.* glycerine, pyrogallol, arsenic, phosphorus. Transfusion of this blood into another animal causes thrombosis, but only if it is first of all defibrinated. There are also diseases in which coagulation does not occur, or occurs only with difficulty. Inflammatory conditions—as pneumonia, pleurisy, rheumatism, etc.—belong to the latter class; whilst hæmophilia, scurvy, purpura hæmorrhagica are instances of the former. In leukæmia the blood coagulates more slowly than under normal conditions; but, contrary to the rule in normal blood, the coagulation is hastened by the introduction of carbon dioxide. The question whether free fibrin ferment is always present in fever has been answered by Hammerschlag in the negative. We owe Wooldridge (1) the credit of showing the most interesting relations between coagulation and infectious diseases. This observer found that injections of solutions of tissue fibrinogen from the thymus gland, with as little alkali as possible, rendered rabbits immune to anthrax. Wright and Woodhead (2), in further investigation of this subject, found that these injections caused, after preliminary destruction of leucocytes, an enormous increase in the number of white cells, and they attributed the immunising action of the fibrinogen to this factor.

H. S. Rolleston and Starling (2) found large amounts of typical cell fibrinogen in the infiltrated lung tissue of pneumonia. The process of immunisation seems to be akin to that of coagulation, for it is held by some that substances which hinder coagulation have the power of paralysing the toxic effects of diphtheria toxin in guinea-pigs (4).

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CHAPTER IV.

THE MORPHOLOGY OF THE BLOOD.

I. *The Red Corpuscles.*—The red corpuscles of the normal adult are for the most part circular, non-nucleated discs, thinner in the centre than at the periphery. This central depression gives them a biconcave appearance when viewed in transverse section. They are smooth, transparent, pliable, soft, and yellow in colour. If we take a fresh drop of blood and cover it with a cover-slip, we see that the red corpuscles at first float about, and then, after a few minutes, arrange themselves in *rouleaux*, whilst leucocytes settle almost at once.

According to Foà (6), the red corpuscles consist of a peripheral hæmoglobin layer; beneath this is a fine network containing granules, which stain well with eosin; whilst beneath this, again, we have the homogeneous cell protoplasm. This agrees with Ehrlich's observation that the red corpuscles outside the circulation show a selective preference for eosin in aniline dyes. A red corpuscle takes up no stain (achromatophile) in the circulation, but when it dies it takes up one of a mixture of aniline dyes—*e. g.* from a mixture of eosin and methylene blue it takes up only the eosin (monochromatophile). This property depends on the albuminous nature of the hæmoglobin. In pathological conditions, and especially in severe anæmias (8, 9), measles, scarlatina, smallpox, typhoid (10), and purpura (11), some of the red cells lose this selective power, and take up two or three colours from a mixture, either diffusely, or in stripes or points; in the last case more especially in their central portion (polychromatophile). Ehrlich (12) regarded these appearances as post-mortem degenerative changes. These necrobiotic changes have been investigated by Maragliano and Castellino (13), who consider that they ought to be divided into two series—the endoglobular and the total changes. The former begin with an apparent enlargement of the central depression, and simultaneous disappearance of the hæmoglobin, which leaves the centre and gradually invades the periphery, until the periphery alone appears coloured. When looked at from the side, such a corpuscle no longer looks like a biscuit, but like the figure "8." Sometimes this egress of colouring matter does not take place uniformly; but peculiar figures appear, such as rods, triangles, reniform or elliptic spaces surrounded by a coloured zone. These colourless endoglobular zones often show amœboid movements, and assume the most divergent forms under the eye of the observer. The movements of the colourless parts become more active as the necrosis continues, digitate processes separate from the chief mass, and, gradually filling the whole corpuscle, give the appearance of a granular mass. The alterations of the whole corpuscle begin later than the endoglobular changes. These begin in human blood in from thirty to seventy minutes, the former only after some three to four hours. At first fine points, or teeth, or rounded knobs, sprout out of the corpuscles, which then increase in size. Amœboid movements gradually become visible, and the corpuscles take on the polymorphous appearances long known under the term poikilocytosis. Small portions gradually separate off from these. They are at first connected by slender bridges with the rest of the corpuscles; but, becoming free, float about in the plasma. Decolorisation takes place simultaneously with the total changes. This starts from some point in the surface, and gradually affects the whole corpuscle. The corpuscle looks like a thin ring from the front, but from the side like a long thin rod, the ends of which are rounded off, thickened, and coloured yellow. From repeated observations (14) of spontaneous and artificial necroses, I can corroborate this description of the processes, with the exception of the last observation, which, doubtless, is seldom seen. The fact that these changes, which can be artificially produced outside the body, actually occur in the blood of different diseases gives them a certain clinical significance, for it would seem to prove that there are certain pathological conditions, accompanied by necrosis of the red corpuscles, and that in these, as Castellino (15) has shown, the cause of the necrosis is the increase of the so-called globucidal power of the plasma. Further, different poisons (chloroform, hydroxylamin, antifebrin, acids and alkalies, extracts of organs) cause the same appearances. The peculiar fenestration of the red corpuscles of the frog, which occurs after lupetidin poisoning, first described by Grüber (16), produces a change morphologically identical with the changes in human blood described above. Maragliano and Castellino have found necrobiotic appearances of the red corpuscles, both endoglobular and poikilocytotic, in cancerous cachexia, tuberculosis, parenchymatous nephritis, etc. The cases in which poikilocytosis was found in fresh blood had a fatal issue. When the changes affect the whole corpuscle the prognosis appears to be bad, whilst the endoglobular changes are seen in less serious and more transitory processes. These changes, then—endoglobular changes and poikilocytosis in fresh blood—are a sign of commencing necrosis of the red corpuscles, and form an important sign of intra-vascular damage to the blood.

The amœboid movements of dying red corpuscles must not be confounded with certain erratic movements often observed in preparations, which have been described by Browicz (17). These belong to the so-called molecular movements, and their physical nature is not understood. In addition to these morphological changes the red corpuscles vary in size, in health and in disease. Authors agree that the red corpuscles are not all of the same dimensions, but they differ somewhat in their estimations of the absolute values. These differences are due partly to the method used, partly to the great variations in the separate red corpuscles, which may be caused by age, state of nutrition, or pathological conditions. In healthy adults the following differences in size have been found :

Welcker (18)	found	dimension	4·5—9·5 μ,	average	7·2—8·1 μ.
Valentin (19)	,,	,,		,,	7
Malanin (20)	,,	,,		,,	7·7
Hayem (21)	,,	,,	6—8·8	,,	7·5
Malassez (22)	,,	,,		,,	7·6

Laache (23) found dimensions 6—9 μ, average 8·5 μ.
Bizzozero (24) ,, ,, ,, 7—7·15
Gram (25) ,, ,, 6·7—9·3 ,, 7·7—8·0

The medium sizes are much the commonest.

Hayem found 12 per cent. small (6—6·6 μ) = "globules nains," 75 per cent. medium (7·5 μ), and 12 per cent. large (8—9 μ) = "globules géants."

Gram found in man 1—12 per cent. small, 74—89 per cent. medium, and 4—23 per cent. large; in woman 3—8 per cent. small, 73—90 per cent. medium, and 5—21 per cent. large.

The influence on the size that some authors ascribe to the effect of sex is, according to Gram, open to doubt. It is different with regard to age. In the new-born strikingly small and strikingly large corpuscles are seen together. Hayem found variations from 3·3 to 10·3 μ. Gram noticed an apparent increase of the average size in travelling from south to north:—Italians 7—7·5, French 7·5—7·6, Germans 7·8, Norwegians 8·5. Some smaller coloured elements of the blood in health and disease have been described by Masius and Vanlair as microcytes. These were found as constant elements of the blood in severe anæmias, and after intoxications and burns. They appear only for a short time, and then disappear; it seems beyond doubt that they are products of disintegration of the red corpuscles. They are much more common in disease than in health, and perhaps are formed in much the same way as the poikilocytes.

The differences in size I have mentioned occur under physiological conditions, but still more under pathological conditions. This is especially true in diseases of the blood and blood-forming organs. In certain processes, such as severe anæmias, new cells—exceptionally small or large—are observed which have not been found in normal blood. Hayem, *e. g.*, describes dwarf-cells 2·2 μ, and giant-cells 12·14 μ.

Ehrlich's results and nomenclature are authoritative with regard to the changes in form and size of the red corpuscles in severe anæmia. He first draws attention to the fact that in these specimens the signs of degeneration and regeneration of the red corpuscles lie side by side. Both processes seem intimately connected with one another, and their mutual relations are of the first importance in giving a prognosis of the case. According to Ehrlich the formation of poikilocytes or schistocytes is the most important sign of degeneration in anæmic blood. Quincke was the first to describe these polymorphous changes in the contour of the red corpuscles in pernicious anæmia, and thought he had discovered a specific sign of the disease. The poikilocytes, however, soon lost this significance, as they were found in other diseases, and it was gradually accepted that they denote some necrosis of the protoplasm of the red corpuscles, which was caused by external injury. Laache and Gräber (27) were of this opinion, whereas Hayem considered them to be young red corpuscles, which were due to a metamorphosis of the hæmatoblasts (platelets). It is now settled through Ehrlich's and Maragliano's investigations that they are the results of fragmentation or segmentation of the corpuscles. The poikilocytes often show depressions, like normal corpuscles, and Ehrlich explains that, as they are a product of the corpuscles, they contain the protoplasm of the blood disc, which has a tendency in a state of rest to take on the typical depressed form of the red corpuscles. Thus the blood-disc breaks up into homologous forms just as fat-drops break up into small spherules. The size of these formations varies between wide limits, between that of the smallest bacteria and that of normal red corpuscles. As a further sign of degeneration in the blood of severe anæmic cases Ehrlich mentions those endoglobular changes of the corpuscles, to which he gave the name "anæmic degeneration." They coincide with those changes that were later called polychromatic degeneration by Gabritschewski (28) and karyolysis by Troje (29), and which finally were characterised by Maragliano as endoglobular necrobiotic processes. Another form of degeneration of the red corpuscles which Ehrlich calls the hæmoglobinæmic belongs to this group. This does not appear as such in anæmic blood, but only after the action of certain poisons on the red corpuscles. It is characterised by the appearance of small drops of hæmoglobin in the body of the corpuscles, which occasionally find their way outside the corpuscles. Heinz (30) found these changes first in the blood of rabbits, which had been poisoned with phenylhydrazin and its derivatives, and thought that he had found a specific sign of poisoning by this group. Ehrlich, however, states that this hæmoglobinæmic form of degeneration is the result of a large number of poisons, and not only the phenylhydrazin group; and I am able to confirm him. In cases of severe anæmia there are always at the same time signs of commencing regeneration in the blood. The most important of these is the appearance of nucleated red corpuscles. Ehrlich considers that these must be divided into two groups: the normoblasts and the megaloblasts. The former are nucleated red corpuscles of the size of a normal corpuscle; their appearance is very characteristic, especially in the dry preparations stained after Ehrlich's method, the body of the cell being stained by the acid dye, whilst the central nucleus takes on the basic dye with exceptional intensity. The nucleus is usually single, but sometimes we see normoblasts with two or three, apparently well-formed, nuclei lying free side by side or separated by a fine bridge of nuclear substance, so that the figure of a trefoil or rosette is formed. Sometimes also we see karyomitotic processes in the nuclei of the normoblasts. Luzet (31) was the first to observe this in a case of so-called 'anæmia pseudoleukæmica infantum.' Later v. Noorden (32), Troje, and Askanazy (33) made the same observation, the last named describing in his case an exceptionally large number of normoblasts in mitotic division, amongst them one trebly divided. Ehrlich's megaloblasts or gigantoblasts, are two to four times as large as normoblasts, but coarser; circular and rich in hæmoglobin. They are said to differ from normoblasts principally in that the nucleus is not ejected from the cell but degenerates in the cell and gradually breaks up. Ehrlich states that they never appear in the blood of adult healthy men or animals; they appear, however, in the blood and blood-making organs of the embryo. Ehrlich, therefore, considers their appearance in an adult patient as a return to the embryonic condition. The normoblasts have a clinical significance as a sign of new blood-formation; they are generally found in varying numbers in the blood of cases of anæmia, and decrease as the quality of the blood improves. More rarely they intrude in larger numbers into the circulation, an appearance that v. Noorden, who first noticed it, called a blood crisis. Such a crisis lasts a varying time, but generally not more than four to six days, and is followed by a perceptible increase in the number of red corpuscles. v. Noorden, *e. g.*, noted an increase from 800,000 to 1,300,000 after a four day crisis, whilst I have noticed an increase from 1,250,000 to 1,730,000 after a five day crisis. The megaloblasts are rarer than the normoblasts, and, according to Ehrlich, their appearance is a sign that the new formation of blood is not normal. When they lose their nucleus they become the so-called megalocytes, large cells rich in hæmoglobin with no depression. Megaloblasts and megalocytes are, according to Ehrlich, diagnostic of true pernicious anæmia. Normoblasts and megaloblasts may undergo poikilocytosis, and Ehrlich considers that this shows the condition to be one of exceptional severity.

THE NUMBER OF RED CORPUSCLES.

Many attempts have been made with the different methods of enumeration, since the time of Welcker and Vierodt, to estimate the normal number of red corpuscles in men and women. The oldest results (Andral 34, Gavaret 35, Becquerel and Rodier 36) cannot be compared with the later results, on account of the difficulties of the methods used, viz. estimation by weighing. At present we have no really sound foundation for an estimation of the absolute number of red corpuscles, because we can only make approximate estimations of the absolute amount of blood in the living body. All the results, therefore, refer only to the number per millimetre which is obtained by the methods in common use. The variations in the numbers given by different authors for the normal number are largely due to the methods used.

The following table gives some of the results obtained for the number of red corpuscles per millimetre in undiluted blood :

TABLE.

Author.	Men.			Women.		
	Average.	Max.	Min.	Average.	Max.	Min.
Vierodt (37)	5,174.000 5,055,000					
Welcker (38)	5,000,000	5,269 505	4,573,346	4,500,000		
Cramer (39)	4,720.400					
Mallassez (40)	4.310,000	4,600,000	4,000,000			
Hayem (41)	5,500.000					
Sörensen (42)	...	5.800.000	4,174.000			
Patrigeon (43)	5,500.000	6,000.000	5,000,000			
Bouchut and Dubrisay (44)	4,192,687	4.899.375	3,399,395	4,165,725	4,698.375	3.306,500
	4,080,113	5,904.375	3,266,250			
Cutler and Bradford (45)	3.000,000					
Laache (23)	4,970.000	...	...	4,430,000		
Helling (46)	5.910.000					
Fridrichson (47)	5.072,000					
Otto (48)	4,990.000	...	...	...	4,584,000	
De Renzi (49)	5,000.000					
Halla (50)	...	5,270.000	4,030.000			
Andreessen (51)	...	7,000,000	5,000,000			
Zäslein (52)	5.010,000					
Neubert (53)	5.603.000					
Ziegler (54)	...	...	...	5,251.000		
Reinl (55)	...	...	...	4.497,300		
Gräber (27)	5.081,000					
Stierlin (56)	5,752,600	...	...	4,994,000		
Reinicke (57)	5.209.667					

A rough average gives 5,000,000 as the normal number of red corpuscles per mm. in men and 4,500,000 in women. The number of the red corpuscles does not show such marked variations as that of the leucocytes, nevertheless many physiological influences—apart from pathological ones—affect it. If the number is increased above the average the condition is called *polycythæmia*. If, however, it is diminished below the normal it is called *oligocythæmia*. This latter term is replaced in clinical practice by the incorrect appellation *anæmia*. It will be well to consider the origin of these conditions before we discuss all the influences causing an increase or decrease in the number of corpuscles.

Origin of Polycythæmia.

It is difficult at the present time to recognise a condition of absolute increase of the red corpuscles without a simultaneous relative polycythæmia, as we are unable to estimate the total amount of blood in the body. The older authors assumed the existence of such a condition, Plethora vera (see above), but relative increase of the corpuscles is often incorrectly included in this term. What is now called polycythæmia refers only to the blood in the circulation, and not to that in the whole body. It is at once obvious that a relative increase of the number of red corpuscles will be caused by an actual increase in the number, or by a diminution of the plasma. The former is doubtless, clinically, less frequent. It plays some part, however, in certain experiments on animals, where, as has been seen, transfusion of blood from one to another causes a true plethora only for a short time, but this soon yields to a condition of polycythæmia ; this, in turn, is merely a transitory appearance, as is shown not only by Worm-Müller's data, but also by those of Quincke (58) and Peters (59), who demonstrated the abnormal increase of destruction of red corpuscles after transfusion in life—both in normal and pathological conditions—and after death. With regard to the question of the influence of artificial polycythæmia on the health of the animal, it may be assumed that in itself it can hardly have a deleterious effect. Transfusion in experiments is, indeed, often followed by death, but this must be attributed chiefly to the artificial plethora, *i. e.* the over-filling of the vessels and consequent increased strain on the heart, for the subsequent polycythæmia is apparently well borne. With this form of polycythæmia, caused by direct increase of red corpuscles, we must contrast the second form, caused by oligoplasmia. All those forces that cause increased output of water from the body must cause polycythæmia unless the red corpuscles are destroyed at the same time. Not only general loss of water but loss from the blood alone, such as is brought about by the so-called lymphagogues (Heidenhain)—substances increasing secretion of lymph—causes thickening of the blood and consequent polycythæmia (Grawitz, 60). Certain thermic influences, such as cold baths (Rovighi, 61; Knöpfelmacher, 62), have the same effect. In none of these cases do we know of the pathological significance to be attached to the polycythæmia. We know, however, by experiment, that far higher degrees can be borne without difficulty than are produced by the above-mentioned causes. Polycythæmia has only a limited pathological significance; it has been observed after great loss of water in heart disease, and other conditions accompanied by congestion, certain poisons, such as phosphorus, carbon monoxide, etc.

ORIGIN OF OLIGOCYTHÆMIA.

For a considerable time we had very little knowledge as to the production of oligocythæmia.

The observations of Tappeiner (63), v. Lesser (64), and Worm-Müller (65) have shown that blood losses in animals up to 3 per cent. of the body-weight, are followed at once by a decrease in the blood-pressure, but that this pressure is soon restored almost to normal. These authors thought that this showed that the loss of fluid was compensated for by vasomotor action or contraction of the vessels. Regeczy (66) opposed this view, chiefly on account of the diffusion which goes on between the tissues and the blood, and assumed that the tissue fluids streamed into the vessels immediately after any loss of blood, so that the normal amount of fluid quickly reappeared, and consequently the blood-pressure became normal. This view was again contested by Cohnstein and Zuntz (67). They showed that it was impossible for the tissue fluids alone to regulate the pressure after a loss of blood, and reverted to the former theory. The value to be attributed to each of these influences may, I think, be conveniently appraised if we enumerate the number of corpuscles in the peripheral vessels of an animal to which a kymograph is applied, and compare the values of blood-pressure and number of corpuscles after the loss of blood has taken place.

A hundred centimetres of blood (*i. e.* about one third of the probable amount of blood in the body) were drawn from the femoral artery of a dog weighing 4180 gr. The carotid was connected with the manometer of a kymograph. The blood-pressure and number of corpuscles were—

Time.	Blood-pressure.	Number of red corpuscles per c.mm.
10.20	149 mm.	7,040,000
10.35 Bled	61 mm.	
10.36	134	7,400,000
10.46	137	6,440,000
10.53	140	4,820,000

In a second experiment on a rabbit only the corpuscles were counted :

Before bloodletting		6,070,000 red corpuscles.
3 minutes after	do.	5,340,000
7 do.	do.	4,940,000
17 do.	do.	2,720,000

We see that the regulation of the blood-pressure cannot be entirely attributed either to the tissue fluids or to vaso-motor action. In the first experiment we can see clearly for how long the restoration of pressure was due to the vaso-motors ; we see that this influence became gradually less and less, for the tissue fluids streaming in restored the original volume, diluted the blood, and approximately restored the original pressure. The question now arises whether the action of the vaso-motors slackening, the old blood-pressure being restored, and the blood having reached its maximum dilution, the capacity of the vessels is, after a certain time, the same as it was before the bloodletting, *i. e.* whether the vaso-motors cease to be responsible for the pressure. I estimated, by Buntzen's method, the amount of blood in a dog before and after bloodletting, in order to determine this. The amounts were 2121·4 c.c. before the loss of blood, and 2178·8 c.c. after. Making every allowance for errors of method, it is probable that the old amount of fluid in the vessels is restored in thirty to forty minutes in an animal in which there is no lack of water in the tissues. The next question to answer is that of the composition of the fluid which enters the vessels. The classical investigations of C. Schmidt (68) showed that a "hyp-albuminosis" of the blood followed loss of blood, and that the lost albumen was replaced by salts from the tissues. For every 100 parts of albumen, 6 parts of soda, or 13 parts of sodium phosphate, or 31 parts of sodium chloride enter the circulation ("Diffusion equivalent," 69). These facts necessitate that oligocythæmic blood should be relatively rich in salts after a loss of blood has taken place. The following experiment is an example:—A rabbit weighing 1370 gr. was bled to the amount of 30 c.c. The number of red corpuscles before this was 3,950,000, and three quarters of an hour later was 2,210,000. The original amount of salt was ·479 per cent. This increased to ·522 per cent. This relative richness of salts can be explained either on the ground that the plasma, whilst remaining the same in volume, has become richer in salts (Runeberg [70]), or that the plasma had a higher concentration owing to an accession of lymph. Hamburger (71) found that the osmotic power of the serum remains constant during the phases of bleeding; this indicates that the fluids entering from the tissues must be richer in salts than the plasma which remains in the vessels.

The following influences must be considered in connection with the question why, after loss of blood, tissue fluid or lymph enters the vessels. An extensive change between two fluids separated by a membrane can occur (if we confine ourselves to osmotic action) only if the chemical constitution of the fluids or of the membrane has altered. Neither of these seems to occur here, for in the case of a rapid loss of blood there is no appreciable change in the blood or the concentration of the plasma, whilst a change in the capillary vessels in this short time is more than improbable. The explanation must therefore lie in so-called vital forces. Such a vital force may exist in the difference of pressure, when the contraction of the vaso-motors begins to relax, between the tissues and the contents of the vessels. This may cause lymph to at once enter the blood-vessels, just as new lymph is formed when the lymph-channels are emptied (cf. 72—75). The observations of Colson (76) and Heidenhain (77) support this view; they found that the lymph flowing from the thoracic duct diminished in quantity when there was a diminution of blood-pressure. The relative richness in salts and poverty in albumen of the lymph explains the difference in the quality of the blood before and after blood-letting, especially as Runeberg has shown that if we increase the pressure, water and salt solutions diffuse more quickly through animal membranes than solutions of albumens. The relaxation of the vessels by means of the vaso-motor nerves, then, accounts for the flow of lymph, which causes a restoration of the original volume of the blood. Whether there is also a secretory activity of the living capillary wall is not yet known.

It is a matter of experience that loss of blood is borne well or badly by different individuals—*e. g.* in adults of middle age better than in children or aged people; in health better than in illness. These differences seem to me to rest on three points: (1) the amount of water in the tissues; (2) the rapidity with which the tissues can give up their water; and (3) the rapidity of the bleeding.

A. The Influence of Physiological Changes on the Number of Red Corpuscles in the Circulation.

(1) *Sex.*—As has been shown, male adults have on the average more red corpuscles than females of the same age. This fact, certified by innumerable observations, seems to be caused by the menstrual flow. Stierlin (78) examined the blood of girls and boys between the ages of nine months and fifteen years, and found on the average that the difference was in favour of the girls (boys, 5,102,108; girls, 5,448,000).

(2) *Age.*—Age is said to have some influence in itself on the blood, apart from the new-born, in whom the blood is affected by special circumstances. Sörensen (89) gives the following table:

Age.	Men.	Age.	Women.
5—8 days	5,769,500	1—14 days	5,560,800
5 years	4,950,000	2—10 years	5,120,000
19½—22 ,,	5,600,000	15—28 ,,	4,820,000
25—30 ,,	5,340,000	41—61 ,,	5,010,000
50—52 ,,	5,137,000		
82 ,,	4,174,700		

Other authors give no such changes, and it seems improbable that age alone does cause any such change, especially if we look at the above table and notice the obvious effect of menstruation between the fifteenth and twenty-eighth years.

The Polycythæmia of the New-born. (Ref. 79—94.)

All writers agree that the number of red corpuscles in the circulation is relatively high immediately after birth ; Hayem found a maximum of 6,262,000, and a minimum of 4,340,000. Otto found ten hours after birth 6,910,000, and fifteen hours later 6,496,000. These high values continue for the first few days. Otto gives the average for the first four days as 6,165,000, Sörensen for the first five to eight days as 5,769,700 ; on the other hand, Bouchut and Duerisay found small values (4,269,911) in fifteen cases from two and a half to fifteen days old, as compared with other observers ; against which Schiff found on the average 5,825,465 red corpuscles in the first fourteen days. The fact whether the umbilical cord is cut early or late has, no doubt, great influence on the blood.

Hayem found 5,087,000 when the cord was divided early, 5,576,000 when the cord was divided after cessation of pulsation. Helot found 5,080,000 and 5,985,347 respectively in these cases. The values are highest in the first few days, and gradually undergo a diminution which, according to Hayem, is directly proportional to the body-weight of the child. According to Schiff this diminution is, however, not a gradual one, but consists of irregular daily variations, the daily maxima and minima approaching nearer and nearer. This is made clear by the following table of Schiff's :

Josefa G—, born April 19th. 1889. Initial weight. 2970 gr.

Date.	Weight.	Red cells.	White cells.	Proportion.	Hæmoglobin.	Daily average.			Remarks.
						Red cells.	White cells.	Hæmoglobin.	
20/4	2840	6,658,000	12,000	1 : 555	105	...	...	...	Light jaundice.
21/4	2790	8,470.000	13,200	1 : 641	115	7,628,000	10,850	107·3	
,,	—	6,786,000	8,500	1 : 798	100				
22/4	2810	6,718,000	8,250	1 : 814	90	6,382,000	7,425	82·5	
,,	—	6,046,000	6,600	1 : 916	75				
23/4	2770	6,486,000	8,400	1 : 772	95	6,071,000	8,000	95·0	
,,	—	5,656,000	7,600	1 : 744	95				
24/4	2840	6,670,000	7,500	1 : 889	102	6,401,000	9,375	95·0	Jaundice diminished.
,,	—	6,132,000	11,250	1 : 544	88				
25/4	2900	4,496,000	10,750	1 : 418	103	4,441,000	15,500	89·5	
,,	—	4,386,000	20,250	1 : 216	76				
26/4	2950	4,920,000	22,600	1 : 218	86	4,676,000	19,925	81·0	
,,	—	4,432,000	17,250	1 : 257	76				
27/4	2950	4,610,000	14.750	1 : 312	86	4,473,000	15,875	83·0	
,,	—	4,336,000	17,000	1 : 255	80				
28/4	3000	5.950,000	20,000	1 : 297	75	5,201,800	19,250	77·5	
,,	—	4.453,000	18,500	1 : 241	80				
29/4	3000	5,040,600	21,500	1 : 234	76	4,609.375	17,500	76·0	Cord cut.
,,	—	4,178,100	13.500	1 : 309	—				
30/4	3080	4,990,600	19,200	1 : 260	—	4,318,750	15,850	—	
,,	—	3,646,800	12.500	1 : 292	—				
1/5	3120	4,753,800	13,000	1 : 366	—	4,319,100	14,100	—	
,,	—	3,884,400	15.200	1 : 255	—				
2/5	3150	4.643,700	17,000	1 : 273	—	4.532,800	17.500	—	
,,	—	4,421,900	18,000	1 : 245	—				
3/5	3170	4,565,600	11,600	1 : 394	—	4,256,000	13,050	78·0	
,,	—	3,946,400	14.500	1 : 272	78				
4/5	3200	4,881,200	9,800	1 : 498	70	4,565,600	9,500	68·0	
,,	—	4.250,000	9,200	1 : 462	66				6/5, discharged.

We see that (1) the number of red corpuscles is greatest in the first few days of life; (2) that in the following days it gradually diminishes; (3) that the daily variations are so large that we only recognise the diminution on taking the average for the day.

Lépine stated that the polycythæmia increased on the first day, but according to Schiff this is only true up to the time when the first nourishment in taken.

With regard to the origin and gradual disappearance of the polycythæmia, all authors agree in considering that the question of the presence or absence of polycythæmia depends upon variations in the concentration of the blood. A child during its first respirations loses large quantities of water (Camerer [95], Preyer [96]); this must increase until nourishment is taken, and can only gradually decrease after continued ingestion of fluid. I do not, however, think that it is proved that there is not an abnormal destruction of red corpuscles, as was originally stated by Hayem. Schiff takes the view that the use of red corpuscles is increased during the first few days on account of the sudden increase of metabolism. "The greater the need of red corpuscles the greater in general is the amount formed, and as the metabolism in the course of the first days is gradually regulated and becomes relatively moderate, fewer red corpuscles are needed, and therefore fewer are formed." From this point of view there is no question of an increased destruction of red corpuscles in the healthy new-born, and I do not know whether any one has ever demonstrated such an increased destruction as, *e. g.*, Worm-Müller did in the case of artificial polycythæmia.

(3) *Nourishment and the condition of nutrition.*—It was maintained that the taking of nourishment caused an increase of red corpuscles, somewhat analogous to the leucocytosis which follows on digestion; thus an increase of 15 to 19 per cent. was said to occur from half to one hour after food (Sörensen) and then to gradually disappear. On the other hand, Vierordt and Duperi (98) found a diminution in the number of red corpuscles after food. The differences found by Sörensen did not much exceed the errors of observation, whilst my own observations rather corroborate Vierordt and Duperi. After a meal the leucocytes increase in number, but the red corpuscles often diminish; this, I think, is due to the dilution of the blood, more especially when fluid nourishment is taken. *Example :*

Before meal	5,553,000	red corpuscles	7,666	leucocytes.
$\frac{1}{4}$ hour after	5,320,000	,,	6,166	,,
$1\frac{1}{4}$,,	5,480,000	,,	8,500	,,
$2\frac{1}{4}$,,	4,733,000	,,	12,000	,,
$3\frac{1}{4}$,,	4,872,000	,,	14,000	,,
$4\frac{1}{4}$,,	4,720,000	,,	10,830	,,

Reinert also has found in a number of cases a diminution in the number of red corpuscles after meals.

Conditions of nutrition, within physiological limits, have different effects on the number of red corpuscles. The blood of muscular and lean people is on the average somewhat richer in red corpuscles and hæmoglobin than that of fat ones (Leichtenstern [99]). This agrees with what we know of the effect starvation has on the number of red corpuscles.

All authors (100—110) agree that abstinence from food causes *no diminution* of red corpuscles; on the contrary, there is apparently—at any rate at first—*an increase* of red corpuscles. A twenty-four hours' fast produces an apparent increase of 400,000 to 500,000 red corpuscles. Reyne starved a dog for twenty-three days, and found that during this time the red corpuscles increased by 2,449,000. v. Hosslin kept a dog for a year on a very low diet, but obtained no diminution of red corpuscles; in fact, the number of red corpuscles was greater than in a similar but well-nourished animal. Lately, however, Grawitz ('Berl. klin. Woch.,' 1895, No. 48) professes to have found that malnutrition produces a distinct, if slight, anæmic effect in man. Kisch, on the other hand, found the amount of hæmoglobin increased in the plethoric form of "lipomatosis universalis." Hayem, too, states that people of weak constitution have fewer red corpuscles than those who are strong. It is a matter of every-day experience, too, that anæmic conditions are very common in a badly nourished population, poor districts, etc., and that an amelioration of the conditions of life of badly nourished, anæmic people induces an increase in the number of their red corpuscles. This is in apparent contradiction to Leichtenstern's view, which I can corroborate from my own observations. Stierlin examined twenty-two children with regard to this point before and after their holidays. On their return fifteen showed an increase of red corpuscles, some of them a considerable increase, whilst one had an increase of 2,320,000. These results do not gainsay the results of the starvation experiments above, they seem to me merely to show that the anæmia of the debilitated and badly nourished is due not so much to starvation as to unhygienic surroundings. Kisch's increase of red corpuscles in the obese is not, according to my experience, invariable. I found in three extremely fat but otherwise healthy patients 4·5 to 4·8 million cells, and in one case 5·2 millions, which leads me to think that Kisch's results were due to the purging effects of the Marienbad waters.

(4) *Menstruation, pregnancy, and lactation.*—The influence of menstruation on the number of red corpuscles might be expected to correspond to that caused by greater or smaller losses of blood, but a diminution of the cellular elements does not always follow menstruation. The explanation of this depends on the facts that the loss of blood is generally spread over a considerable time, and that it is often of inconsiderable degree. Consequently even a slight increase of the corpuscles may occur. This is especially the case in chlorotic girls. It was formerly taken for granted that a plethora, *i. e.* polycythæmia, existed during pregnancy, for it was thought that the blood in these cases was bound to contain more nourishment than normal blood. On the other hand, some of the older authors, on the basis of their investigations, asserted that the contrary was true, viz. that in pregnancy there is a diminution in the number of the red corpuscles in the blood. Gynæcologists (112—120) have been divided in their views on this question; but the present view seems to be that pregnancy in itself has no direct influence on the blood. As, however, we often observe anæmia during pregnancy, especially in the lower classes, the cause must lie in other circumstances, especially in the social misery undergone in this condition by the patients of the class that enter lying-in hospitals. This view is confirmed by my own observations on pregnant patients who have undergone treatment for various causes.

The loss of blood during *confinement* causes a diminution of red corpuscles according to its intensity. In uncomplicated cases the number soon returns to the normal (ten to fourteen days). Some have noted a slight increase of red corpuscles during the actual parturition and shortly after, and rightly attribute this to the loss of water the patient always undergoes.

How far lactation, as such, affects the number of red corpuscles is doubtful, as in any given case the relations are often complicated by other influences.

(5) *Time of day and season of year.*—The variations observed during the day are not constant, and, such as they are, can be explained by other circumstances, *e. g.* the ingestion of food and fluid.

Mallassez' statement that in winter the number is greater than it is in summer, probably also depends on similar influences.

(6) *Climate.*—(*a*) *High altitudes.*—Viault (121) made the interesting observation on himself that whilst a mm.^{3} of his blood contained five million red corpuscles when in Lima, the number increased to seven millions after fourteen days in the Cordilleras, and after three weeks to eight millions. In other people he found 7·3 to 7·9 millions; in short, a distinct polycythæmia existed. Animals at this height (4392 m.) also showed a distinct increase in the number of red cells. These observations have been confirmed (122—126). Köppe gives the following table showing the altitude and average number of red corpuscles:

Author.	Place.	Altitude.	Average number of red corpuscles.
Laache	Christiania	—	4·974 million
Schäfer	Göttingen	148 m.	5·225 ,,
Reinert	Tübingen	314 ,,	5·322 ,,
Stierlin	Zürich	412 ,,	5·752 ,,
Köppe	Auerbach	400—500 ,,	5·748 ,,
,,	Reiboldsgrün	700 ,,	5·970 ,,
Egger	Arosa	1800 ,,	7·000 ,,

Egger (122) noted also that the amount of dry residue of the serum did not alter, and that the amount of hæmoglobin increased with the red corpuscles, but not proportionately, as at first the amount was rather less. The original number is soon reproduced both in man and in animals on descending from these altitudes. Köppe maintains that the total volume of red corpuscles (obtained by the hæmatocrite) does not alter.

These observations, especially the want of proportion with the hæmoglobin, made it improbable that the increase of red corpuscles was due to any increased concentration of the blood caused by the dryness of the atmosphere. It was consequently assumed that a new formation of red corpuscles took place, more especially as the appearance of microcytes was noted (Mercier [125]). Miescher (127) is not convinced that the explanation that this is due to the diminished atmospheric pressure causing diminished oxidation of the blood is the true one. In Arosa, according to Hüfner's tables, the saturation with oxygen is only $\frac{1}{100}$ part less than it is on the plain. Miescher, therefore, refers to the unequal aëration of different parts of the lungs, and is of opinion that whereas the better aërated portions take up a sufficiency of oxygen within wide variations of pressure, the badly aërated portions cause the effects of slight difference of pressure to be perceptible according to the degree of saturation with oxygen. New formation of corpuscles takes place normally where the pressure of oxygen is low (venous capillaries, Ziegler); in view of this an increase of blood formation would result if the pressure of oxygen in the blood is diminished in consequence of the diminished pressure of the air and the insufficient aëration. There are many objections to this explanation, above all the fact (Grawitz [128]) that clinically we do not see any signs of new formation of red corpuscles on removal to high altitudes, or of destruction of red corpuscles on a return to low levels. Köppe has pointed to a relative smallness in the size of the red corpuscles in high regions, and sees in this a sign of regeneration; he holds that this explains his observation mentioned above, that the total volume of the red corpuscles is unaltered. We should expect from our other clinical experiences to find a large number of normoblasts if regeneration occurs, and some jaundice on return to the plains if destruction takes place. As we find neither normoblasts nor jaundice, Grawitz returns to the old view of Viault that the polycythæmia is due simply to the concentration of the blood caused by the dryness of the atmosphere in these high altitudes. It seems, however, doubtful if this is a satisfactory explanation (Zuntz [129]), though we must agree with Grawitz in discarding the ideas of regeneration and destruction. The experiments, especially of Czerny (130), controvert him. When this author found polycythæmia due to concentration of the blood, it was always associated with a considerable loss in body-weight, which was due to the loss of water. The percentage loss was approximately the same as the percentage increase of red corpuscles. Thus in a cat weighing 416 gr. the number of red corpuscles in a mm.^{3} was 7·09 millions. After the cat was "dried" for six days, the weight was reduced by 45·9 per cent., and the number of corpuscles became 10·266 millions, *i. e.* was increased by 44 per cent. On removal to a high altitude, then, if this explanation were true, the body-weight ought to decline; but exactly the opposite occurs (Wolff [124]). The loss of water from the body is not supplied altogether by the blood, the tissues suffer at least as much; this fact makes Grawitz's explanation insufficient, though at the same time concentration of the blood must be one of the several causes of the polycythæmia. What these other causes are, we do not know; we might perhaps suggest an abnormal division of the red corpuscles in the system, or see in this polycythæmia, and other temporary forms of increase of red corpuscles, an analogy to leucocytosis. Lately, Fick ('Pflüger's Arch.,' Bd. lx) has suggested that the polycythæmia is due to a prolongation of the life of the individual red cells.

(*b*) *Sea climates.*—Observations on this point do not exist in sufficient numbers. The only ones I know of are those of Marestang (131), who during a sea voyage, in examining the blood of sixteen sailors, found an increase of red corpuscles in fourteen. This is of interest when compared with the results of high climates (Rollet [132]). Diminished density of air, we have seen, causes increase of red corpuscles, and now increased density seems to have the same effect. Rollet tries to explain this apparent paradox:—"The increased reduction of hæmoglobin in the blood flowing through the tissues causes a stimulating effect on the activity of the blood-forming organs." It would be desirable to make systematic observations so as to place this matter on as sure a footing as Miescher and his school have done for high altitudes.

(c) *Tropical climates.*—In contrast to the beneficent effects of high altitudes and the sea, the tropics are said to cause *anæmia*, especially in people who are not acclimatised. Of late years, however, new observations (133—135) have shown that the climate in the tropics has in itself no influence on the blood, but that the anæmia which occurs in Europeans is due to other causes. There are many pathological conditions at hand which are quite sufficient to account for anæmia (malaria, bilharzia, etc.).

(7) *The influence of race.*—Whether race, as far as healthy people are concerned, has any influence on the number of red corpuscles, seems more than doubtful. Hayem examined an Esquimaux and two negroes, and found the same values as in Europeans.

B. The Influence of Therapeutic Effects on the Number of Red Corpuscles.

Under this heading we include the influences which certain drugs and certain physical causes have on the blood. The former must be divided into two parts, one class containing drugs which probably affect the formation or destruction of red corpuscles (*e. g.* iron and mercury), and the other including those which merely affect the concentration of the blood and in this way the number of red corpuscles (diuretics and laxatives).

(i) *Iron.*—It is an undoubted fact that this metal exercises a favourable effect on the red corpuscles and hæmoglobin of the blood in certain clinical forms of anæmia, but we do not know by what means. In *health* it appears that iron causes *no alteration in* the blood (Cutler and Bradford [137]), though Fenoglio (136) states that he has found an increase in the number of red corpuscles in health. The action of iron in anæmia, and especially in chlorosis, has become almost proverbial. Many authors have given innumerable examples. I give three of my own:

1. M. S—, age 16; nurserymaid. Chlorosis.

Date.	No. of red corpuscles.	Hæmoglobin (Fleischl).
February 28th	5,000,000	22 per cent.
	Iron in the form of Blaud's pills was given with the following result:	
March 12th	4,200,000	38 per cent.
,, 18th	4,220,000	38 ,,
,, 26th	5,512,000	40 ,,
April 2nd	4,850,000	50 ,,
,, 9th	—	60 ,,
,, 15th	—	65 ,,
,, 23rd	—	70 ,,
May 7th	4,950,000	82 ,,

2. M. F—, age 22; milliner. Chlorosis. Treated for the first three weeks by weekly bloodletting 50 to 70 c.c., then with arsenic and iron.

Date.	No. of red corpuscles.	Hæmoglobin.	Body-weight.
October 24th	3,740,000	20 per cent.	50·9 kg.
,, 31st	3,800,000	25 ,,	52·5 ,,
November 7th	—	30 ,,	53·0 ,,
,, 15th	Fowler's solution		
,, 27th	4,200,000	30 ,,	—
December 1st	3,400,000	35 ,,	—
,, 6th	3,900,000	—	57·8 ,,
,, 22nd	4,000,000	35 ,,	—
,, 27th	Oxalate of iron		
January 2nd	3,700,000	45 ,,	59·2 ,,
,, 8th	—	50 ,,	60·0 ,,
,, 14th	5,000,000	65 ,,	60·0 ,,

3. K. M—, age 55; single. So-called primary anæmia gravis without known cause. In dry preparations microcytes and megalocytes, normo-, megalo-, and poikilo-blasts.

Date.	No. of red corpuscles.	Hæmoglobin (Gowers).	Body-weight.	Remarks.
Admitted July 5th, 1893; discharged Sept. 12th, 1893.				
July 6th	1,200,000	26 per cent.	—	
,, 20th	1,500,000	25 ,,	—	Venesection to 50 c.c.
,, 29th	1,900,000	30 ,,	—	Epistaxis.
Aug. 3rd	1,054,000	30 ,,	—	Excess of albuminous food.
,, 14th	1.250,000	32 ,,	—	Excess of fatty food.
,, 19th	1,260,000	35 ,,	45·3 kg.	Ditto.
,, 27th	1,450,000	40 ,,	47·5 ,,	Ditto.
Sept. 2nd	1,800,000	40 ,,	47·7 ,,	Ditto.
,, 10th	2.200,000	40 ,,	50·0 ,,	Discharged.
Readmitted July 2nd, 1894; discharged Aug. 18th, 1894.				
July 3rd	1.200.000	28 per cent.	43·2 kg.	Sol. arsen. Fowleri.
,, 17th	900,000	30 ,,	44·8 ,,	Ditto.
,, 23rd	1,390,000	30 ,,	44·5 ,,	Ditto.
Aug. 1st	1,400,000	32 ,,	46·1 ,,	Ditto.
,, 9th	1,800,000	35 ,,	—	Ditto.
,, 16th	2,075,000	35 ,,	47·0 ,,	Discharged.
Readmitted Nov. 29th, 1894; discharged March 23rd, 1895.				
		(Fleischl).		
Nov. 29th	1,400,000	20 per cent.	—	Ferratin.
Dec. 10th	940,000	20 ,,	47·9 kg.	Profuse epistaxis.
,, 27th	850,000	—	—	Ferratin discontinued.
1895				Sol. arsen. Fowleri.
Jan. 12th	900,000	—	—	Bleeding ceased.
,, 19th	1,050,000	—	47·3 ,,	
,, 26th	1.200,000	—	46·2 ,,	
,, 31st	1,800,000	32 ,,	44·6 ,,	
Feb. 6th	2,300,000	—	—	
,, 19th	2,900,000	—	—	
,, 27th	3,200,000	38 ,,	—	
Mar. 6th	3.320,000	33 ,,	48·2 ,,	
,, 14th	3,600,000	38 ,,	—	
,, 20th	3,560,000	40 ,,	—	Discharged.

Tables 1 and 2 are good examples of the blood-forming capacities of arsenic and iron. In both cases the administration of iron and arsenic is followed by a primary diminution of red corpuscles; the numbers then gradually increase to the normal. The hæmoglobin in both cases, on the other hand, begins at once to increase in amount. The venesection in Case 2, recommended by Wilhelmi (138), appears to have had no appreciable influence on the blood, although the weight increased.

Case 3 is instructive. A small amount of success was obtained during the first stay in the hospital by placing the patient on a fatty diet. During the second stay, which was short, arsenic had a favourable effect : this was much more marked on the occasion of the third admission. Ferratin was discontinued on account of constant nose-bleeding, and the epistaxis never reappeared. These observations agree with those of other authors, and show that iron has a very favourable influence on some, but not all, cases of anæmia, and more especially upon chlorosis. It generally happens that the number of red corpuscles diminishes somewhat, directly after the commencement of a course of iron, whereas the hæmoglobin either remains stationary or shows a slight increase. In the following weeks the number of red corpuscles increases more rapidly than the amount of hæmoglobin. This is true for all, even spontaneous blood regenerations, and is not, as many think, characteristic of chlorosis.

The theory of the action of iron in anæmia is still obscure. The theorists (Kobert [139], Bunge [140]) hold that the inorganic preparations of iron are not absorbed in the body, and that only the iron of certain nucleo-albumins, such as exist in milk, corn, eggs, etc., are absorbed. The clinical experience of the effects of the inorganic salts is overwhelming. Bunge suggests that the iron of this food combines with the sulphuretted hydrogen in the intestine on account of the increased putrefaction which is said to occur in these cases (Andrew Clark), and that in this way its absorption is prevented. Bunge thinks that inorganic iron, given medicinally, unites with the sulphuretted hydrogen, and therefore protects the iron in the food. Clever as this theory is, further experience has shown it to be unsound (v. Noorden [141]). It has been shown, in the first place, that abnormal putrefaction does not occur in chlorosis (Rethers [142], Mörner [143]); and further, that inorganic salts of iron are absorbed ; these are not secreted by the kidneys, but are deposited in the liver and spleen, and then gradually reappear in the intestinal secretion. The way in which iron acts in chlorosis is, then, unknown. Some speak of a "stimulating effect on the marrow of bones;" this is not an explanation, but a mere circumlocution.

(ii) *Arsenic.*—We have seen that arsenic is efficacious in the treatment of grave anæmias. It is often given in conjunction with iron. Its action has been repeatedly investigated, but the results are not uniform. Cutler and Bradford found that Fowler's solution caused a diminution of red corpuscles when administered to healthy persons. Stierlin and Delpeuch (144) confirmed this. Fenoglio, however, found an increase of red corpuscles and an increase of hæmoglobin. We have a large number of observations of the effect of arsenic in anæmias, especially in pernicious anæmia and leukæmia. The worst cases of anæmia, that is those which are not amenable to treatment by iron, improve with arsenic. In the worst forms of tropical malaria quinine is ineffective, whereas arsenic has a beneficial effect on the constitution of the blood.

(iii) *Mercury.*—The influence of mercury on the number of red corpuscles is small when compared with that of the two previous drugs. Keyes (145), and Leichtenstern and Wilbouchewitsch (146), state that mercury causes a slight increase of red corpuscles. The former finds this even in healthy cases. The later observations of Bieganski (147) are to the same effect; he found that in syphilitic blood the number of red corpuscles, otherwise normal, underwent considerable variations on the ingestion of mercury. These he attributes to alteration in the concentration of the blood. The amount of hæmoglobin is apparently always increased; where, however, large quantities of mercury have been taken we often find anæmia, and not only is the number of red corpuscles decreased, but we find destructive and degenerative changes. Former observations do not confirm this; thus Galliard (148) examined the blood of two non-syphilitic patients who were not anæmic, and found that a diminution in the number of red corpuscles occurred at first, but that this was followed by an increase. Others (149—152) find a constant increase. Lezius (153) finds that inunction of mercury has no influence at all on the number of red corpuscles. The severe consequences caused by acute or chronic mercury poisoning are naturally marked by changes in the blood. The resulting anæmia does not always originate in the same way; this is true also for the anæmia found in professional users of mercury (mirror silverers, etc.).

(iv) *Lead.*—Lead is seldom used in internal therapeutics, but its effect is of great importance on account of the frequency of lead poisoning. Mallassez (154) examined the blood of a large number of cases, and found a diminution of red corpuscles varying from 3·7 to 2·2 millions; whilst I have found in two cases 3·4 and 2·8 millions. Riegel's (155) experiments on the toxic action of lead preparations have shown that animals suffering from chronic lead poisoning lose their appetite after ten to fourteen days, and emaciate. This circumstance may perhaps explain the appearance of anæmia, especially as we know, from the investigations of Kussmaul and Mayer (156), that severe anatomical disturbances of the gastric glands may result in consequence of chronic saturnism, and that diseases of the gastric mucous membrane may cause severe anæmia (Henry and Osler [157], and Kinnikut [158]). Another explanation is given by Hayem. He attributes the diminution of red corpuscles to the direct action of the lead leading to an impaired vitality of the red corpuscles.

With regard to the blood in lead anæmia, I must note that, as far as my experiences go, it is often of the so-called "chlorotic" character. If this term be allowed to pass, there is a lead chlorosis with an approximately normal number of red corpuscles and a diminished amount of hæmoglobin. The significance of this condition as a sign of regeneration of the blood has been mentioned above. The appearance of megaloblasts has repeatedly been described and laid stress upon (Mallassez) in the severe forms of lead anæmia or chlorosis.

(v) *Silver, copper, zinc, cadmium, antimony, manganese, chromium, tin, bismuth, gold.*—The effect which the heavy metals, therapeutically or as poisons, have on the blood is still partially unknown, but we may expect that both the appearances in the blood and the method of action in chronic tin poisoning will resemble those in chronic mercury or lead poisoning.

We now come to a long list of bodies that affect the blood indirectly by inducing changes in the amount of water in the body.

(vi) *Diuretics, laxatives, and diaphoretics.*—It is obvious that all those substances which induce loss of water, whether through the skin, kidneys, or intestines, must affect the composition of the blood. If a large amount of water is quickly lost, then a perceptible concentration of the blood must result. If the loss is slow or the amount moderate we may not be able to perceive a difference with our present methods.

(vii) *Cod-liver oil and kefir.*—It has been positively affirmed that these substances increase the number of red corpuscles (Cutler and Bradford, Theodoroff [159]); such a result can hardly be due to a specific action, but must depend on the improved condition of nutrition which this brings about.

(viii) Cold baths cause an increase of red corpuscles (160—163). Differences of a million corpuscles have been noted. Winternitz (162) gives one case of an increase of 1·860 millions. The fact of the existence of a polycythæmia due to cold may, then, be taken as demonstrated; the explanations, however, differ. Most observers, including Grawitz (164), consider it to be the result of a concentration due to the action of the vaso-motors, and this would seem to be the correct interpretation. Winternitz, however, falls back on the theory which he enunciated to explain the increase in the number of white corpuscles which occurs under the influence of cold; he believes that the red corpuscles appear in the blood from organs where they were previously stagnant. Cohnstein and Zuntz (165), who are supported by the results of experiments, consider this theory to be untenable.

C. The Influence of Different Pathological Circumstances on the Number of Red Corpuscles.

(1) *Acute cachexia from infectious diseases.*—It is well known that healthy persons may become anæmic after an acute or chronic infectious disease. If losses of blood have occurred during the illness the fact is at once explained; but we often see anæmia, *e. g.* after pneumonia or typhoid, where there has been no loss of blood, and we are driven to assume that there has been an increased destruction of red corpuscles during the illness. Certain clinical observations seem to corroborate this, such as the demonstration of toxic decomposition products of albumen in fever (166—168), of increase of urobilin (169, 170) and of potassium salts (Salkowski [171]) in patients suffering from fevers. An enumeration of the red corpuscles during fever does not, however, corroborate this view, for if blood has not actually been lost the number of red corpuscles is found to be normal, or even increased. In spite of this there is no doubt that during the fever of, for instance, pneumonia, an increased destruction of red corpuscles takes place. This is shown on the one hand by direct observation on bringing together pneumonic serum and red corpuscles, and on the other hand by the greenish colour of the former, which according to Maragliano is due to altered hæmoglobin. If the above enumerations, then, are correct, there must be some influence at work, in addition to the increased destruction of red corpuscles, which prevents the production of oligocythæmia. I think that some part in this is played by the oligoplasmia which, as Steindler (172) has shown, is present in the majority of cases of acute infectious diseases. There can be no doubt that during the course of these diseases the water economy of the tissues is considerably affected; if the normal amount of water is restored on convalescence, then the absolute oligocythæmia becomes a relative oligocythæmia. In addition to the increased globucidal action of the serum and occasional losses of blood, two influences seem to me of importance as regards the increased destruction of red corpuscles. These are the

tissue destruction, and the absorption of the toxins formed by the micro-organisms; for it has been demonstrated that both of these can cause destruction of red corpuscles.

Results of enumeration (173—181) show that the number of red corpuscles is sometimes slightly diminished, but often normal and sometimes even increased, provided that there are no complications. Boeckmann's summary that the number of red corpuscles in fever is in inverse proportion to the height of the temperature is certainly untrue.

(2) *Chronic cachexias.*—So many different pathological conditions come under this heading that we can hardly expect the resulting anæmic conditions to have a uniform character. They seem, however, as far as we can say, to be caused in the same way as in acute diseases. Thus increased globucidal power of the serum, the tissue waste, occasional loss of blood, the defective formation of new red corpuscles, and alteration in the water economy of the tissues, play some part in the matter. With regard to the last, Grawitz (182) showed that injection of extract of cancer nodules caused a flow of lymph into the blood-vessels; and Strauer (183) found that the number of red corpuscles progressively diminished in cases of cancer where there was no hæmorrhage. We cannot, however, say that these are the only influences which cause anæmia in chronic cachexias (*e. g.* tuberculosis, cancer, leukæmia, syphilis, etc.), especially as, *e.g.* in leukæmia, the increased fragility of the red corpuscles may be an additional cause of the origin of oligocythæmia.

(3) *Poisons.*—The substances classed as poisons differ considerably in their influence on the blood. One group certainly has no influence, *e. g.* the inorganic acids and alkalies; a second increases the number of red corpuscles, *e. g.* phosphorus; and a third diminishes the number, *e. g.* pyrogallol.

(*a*) *Phosphorus.*—Taussig (184) first discovered that there was often an exceptionally large number of red corpuscles during the first few days of acute phosphorus poisoning. He found, *e. g.*, at first an increase to 8·65 millions, whilst the number became normal in the next two to three days; v. Jaksch (185) confirmed him, and found also that there appeared to be *no increase of albumen* in the blood in spite of the polycythæmia. v. Jaksch does not consider that the loss of water due to vomiting is a sufficient explanation of this. Two observations of my own showed an increase of red corpuscles, but in these I believe the polycythæmia was in part at least due to frequent vomiting. In the first case there was continuous vomiting during the first two days, during which the number rose to 6·5 millions, but during the next three days it returned to the normal. In the second case in which the patient vomited profusely during the first two days the number of red corpuscles was 7,900,000. Vomiting then ceased, and in two days the number was normal.

(*b*) *Coal gas.*—I had the opportunity of examining the blood of a married couple poisoned by coal gas, and in whose blood carbonic oxide was demonstrable. I found a distinct polycythæmia (6·63 and 5·7 millions). On examining the blood of the first case, obtained by venesection, by Bleibtreu's method, I found a high degree of oligoplasmia (only 29·3 per cent. of serum). Arthur Latham working in my laboratory, and Münzer and Palmer (186), have obtained similar results (5·7 million red and 13·300 leucocytes). Polycythæmia, then, seems to occur in carbonic oxide poisoning. The cause I do not know; in my cases there was no vomiting nor other cause for loss of water.

(*c*) *The poisons which lead to the formation of methæmoglobin.*—The number of bodies having this action in men and dogs is large: in contrast to the previous poison, they cause a diminution in the number of red corpuscles. Whether they first break up the stroma of the red corpuscles and alter the escaping hæmoglobin, or whether the hæmoglobin is altered in the cells and the latter then break up, does not affect the appearance of the blood. We may take *pyrogallol* and *pyrodin* as types of these poisons. Silbermann (187) asserts that continued injections of the former produce, in animals, a very marked and severe anæmia. Pyrodin has been shown to cause similar results (188—196). These substances hardly come into consideration in the pathology of man, but certain medicinal bodies in use, especially chlorates, antifebrin, and phenacetin, lead to the formation of methæmoglobin and progressive destruction of red corpuscles if given in large doses, so that if death does not occur an anæmia of varying degree results.

It seems that in dogs, and probably also in men, death from acute poisoning with chlorates is due not to destruction of red corpuscles, but to failure of the power of the blood to combine with oxygen; for in my experiments (191) the animals, after intense poisoning with this substance, showed no diminution of red corpuscles before they died. If life is prolonged a progressive diminution of the red corpuscles occurs, and at the same time a leucocytosis appears. Brandenburg (192) has published a fatal case of this kind in which the number of red corpuscles sank from 4·3 to 1·6 millions. The leucocytosis was at first 20,000, at the end of the experiment 15,000. Lately Krönig ('Berl. klin. Woch.,' 1895) has described a case of phenacetin poisoning in which there was a similar destruction of red corpuscles with oligocythæmia during life.

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II. The White Corpuscles and the Platelets.

The white corpuscles, when freshly examined in an indifferent fluid, are colourless globular cells, and usually show no nucleus. On the addition of water or dilute acetic acid the cells swell somewhat, the body at first becoming more granulated and then clearing up, whilst one or more nuclei, sometimes irregularly shaped, become visible. These cells form a constant constituent of the blood, and were first discovered by Nasse in 1835. As far as our knowledge goes, the physiological significance of the leucocytes is of a very varied nature. One of their most important functions relates apparently to the nutrition of the organism. The leucocytes probably take some part in the process of oxidation. They are mostly formed during extra-uterine life, and occur chiefly in the lymphatic glands, from which they emerge as mononuclear lymphocytes. After a certain time they change, in the circulation, into the polynuclear form (Löwit) : how this change comes about is not yet clear; Löwit considered it a sign of degeneration, whereas Arnold thought it was due to a progressive development. Mitotic division of the cells is observed in the normal blood of man and of mammals, and has been frequently noticed in certain pathological conditions, such as leukæmia. Different classifications have been proposed from time to time of the white cells of the blood. Thus Virchow and after him Ehrlich (with his pupil Einhorn) have attempted to classify the leucocytes according to their place of origin. Virchow considers that the small mononuclear corpuscles have their origin in the lymph-glands, whilst the large mononuclear arise in the spleen. He calls an increase of the former Lymphæmia, an increase of the latter Splenæmia. Einhorn distinguished between small and large lymphocytes, myelogenous (eosinophile) and similar cells, which he thought were formed partly in the marrow and partly in the spleen. The latter he again divided into large mononuclear, the so-called transitional cells, and the polynuclear corpuscles.

Löwit selected the structure of the nucleus as a basis for classification, and distinguished between large and small mononuclear cells, polymorphous and polynuclear cells. Hayem divided the leucocytes into the following four classes:—(1) small round-cells with a large nucleus and a narrow non-contractile layer of protoplasm; (2) somewhat larger cells of similar structure, but with contractile protoplasm; (3) spherical contractile cells with a lightly granulated protoplasm which is refractive; and (4) cells similar in appearance with shining or blackish granules. Such classifications were founded almost wholly on morphological peculiarities until Ehrlich proposed to differentiate the leucocytes by their microchemical relations towards mixtures of aniline dyes.

Ehrlich's classification is as follows:

(1) *α-granulation or eosinophile.*—Corpuscles, the bodies of which are characterised by a relatively coarse granulation. The granules take up only acid from a mixture of acid, basic, and neutral dyes. In mammals, according to Ehrlich, these cells are formed chiefly from the bone marrow.

(2) *β-granulation.*—Corpuscles whose body is characterised by fine granulation. These granules are stained by *acid and basic* dyes (amphophile). They are found in human bone marrow.

(3) *γ-granulation or mast cells.*—Cells with a finely granular protoplasm; they are *basophile, i. e.* the granules take up only the basic dye.

(4) *δ-granulation.*—These consist mostly of mononuclear cells, and are basophile.

(5) *ε-granulation* or *neutrophile* cells are the most numerous of all, and are especially fragile; they take up only the neutral dye.*

As none of the above classifications is satisfactory from a clinical point of view, the cells are usually classified according to both their morphological and microchemical characters, thus:

(1) Eosinophile cells.
(2) Neutrophile ,,*
(3) Basophile ,,
(4) Mast cells.
(5) Marrow cells.

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* They stain faintly with eosin.

(1) *The eosinophile cells.*—These have very different relations according to their cell structure. The cell body varies in size between that of a small lymphocyte and that of a large corpuscle. The marrow cells may also be eosinophile. The nucleus of the eosinophile cells is not of uniform structure, but the majority belong to the polymorphous or transitory form. They are all characterised by the presence of granules in the cell body which take up the acid dye from Ehrlich's mixture. The number and size of these granules are very variable, and transitions into the form of β-granules (which take up methylene blue as well as eosin from the mixture) have been observed. A very important position has been given to the eosinophile cells in the hæmatological literature of the last few years. In spite of the fact that the origin and significance as regards metabolism of these cells is unknown, it has been asserted that certain diagnostic and prognostic conclusions can be drawn from an increase or diminution in their number in the blood. The number of these statements is very large, but Neusser (2), who attempted to found a complete nosological system on the basis of the relative numbers of these cells, seems to have out-Heroded Herod in this respect. It is generally held that the eosinophile cells should be regarded as the matured form of the different kinds of leucocytes. The considerable size of these cells and the poverty in chromatin of their nuclei favour this view. The nature of the granules is still uncertain: Ehrlich considered them (and all forms of granules in the leucocytes) to represent the products of a specific secretory action; Weiss (3) found that they gave the "Furfurol-reaction," and held that they were therefore of an albuminous nature. Later investigations of Posner (4) and Kossel (5) have confirmed this view. More recently Barker (6) states that he has demonstrated that they contain iron. We do not know how albuminous bodies in the form of drops or granules are formed in the cells, but I might suggest that as albumens require a salt solution of a certain concentration for their solution, the inflated appearance of the cells is due to the precipitation of albumens in consequence of the excess of water taken up by the cell. The

most important writings on the subject of the number of eosinophile cells in health and disease are those of Ehrlich (7), Schwarze (8), Gollasch (9), Fink (10), Gabriezenski (11), Müller and Rieder (12), Rieder (13), Neusser (14), Weiss (15), Hock and Schlesinger (16), Canon (17), Grawitz (18), Okinschitz (19), Botkin (20), and Zappert (21), the last being the most exhaustive. The eosinophile cells of the blood vary in health between ·67 and 11 per cent. of the total number of leucocytes. The absolute numbers, according to Zappert, are between 55 and 784 per c.mm. Relatively high values are physiological in children up to thirteen or fourteen years, whilst variations of the number of these cells are as great in the aged as they are in adults of middle age. Menstruation and pregnancy have no inflence on the number. The amount varies generally between 2 and 6 per cent. in leukæmia. There is often an increase in chlorosis and severe anæmias; but sometimes there is a diminution, which, however, has no diagnostic or prognostic value. Heart disease, compensated and uncompensated, generally shows normal values; whilst a diminution is sometimes observed in pulmonary tuberculosis associated with fever. An increase of these cells generally occurs in bronchial asthma and emphysema, especially in the former; in affections of the liver and kidney, sometimes in functional neuroses and a large number of skin diseases. There is generally a diminution in malignant disease, whilst in infectious diseases with high fever, especially croupous pneumonia, we get a distinct decrease, which may lead to the total disappearance of the cells. We have, further, a number of data founded on an insufficient number of observations; thus Botkin found that injections of tuberculin caused a leucocytosis, but a diminution of the relative number of eosinophile cells. This observation is easily explained by the fact that in inflammatory leucocytosis the cells that appear in increased numbers in the blood are always neutrophile. After the leucocytosis has subsided the number of eosinophile cells is said to return to the normal. Starvation increases the number (Okinschitz). In sarcoma an increase has sometimes been observed. To sum up, I am convinced, both from my own observations and from a study of the whole voluminous literature of the subject, that there are only two regular and constant phenomena, so far as these cells are concerned. These are—(i) The increase of eosinophile cells in the blood in bronchial *asthma*, and

(ii) The diminution and total disappearance of these cells during the course of croupous *pneumonia*.*

The reappearance of eosinophile cells in the blood in the latter disease may be regarded as a sign of the probable approach of the crisis.

(2) *The neutrophile cells* always constitute the great proportion (70—80 per cent.) of the leucocytes in normal blood. The cells of exudation fluids, *e. g.* pus, and the white cells of the blood in leukæmia are also mostly neutrophile. The size of their cell bodies and form of their nuclei are subject to great variations. The size of the greater number is somewhat larger than that of a red corpuscle ; the body is dotted with fine granules, and the overwhelming majority belong to the polymorphous or to the so-called transitional form. In the latter case they show in one or more places depressions of varying depth in the nucleus. It is these cells that are responsible for the increase in leucocytosis. The majority of lymphocytes also, large and small, usually have neutrophile nuclei. The neutrophile cells, and amongst them especially the polynuclear and transitional cells, have the power to seize foreign bodies which enter the blood (phagocytosis). Such foreign bodies may be very different in nature. The products of disintegration of the red corpuscles, melanin granules, and altered hæmoglobin are found enclosed in these cells in many processes accompanied by destruction of red corpuscles (*i. e.* melanæmia, malaria, melanotic tumours, certain forms of poisoning). Bodies which have entered the blood from outside the body, *e. g.* micro-organisms, or insoluble substances added to the blood, *e. g.* coal-dust, have also been found within these cells.

(3) *Basophile cells.*—These are generally about the size of a red corpuscle with only one circular nucleus, and contain relatively coarse granules—smaller, however, than

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* The number would appear to be increased in cases of *Trichina spiralis* (Thayer).

the granules of eosinophile cells—in their protoplasm. Opinions are divided as to their appearance in the blood. Canon says they are constantly present, especially in children. It seems to me doubtful, however, whether these cells occur in the blood of healthy adults. Ehrlich thinks they do not; whilst I have found them only in leukæmia, and then in very small numbers.

(4) *Mast cells* belong morphologically to the transitional or to the polynuclear form, and are sometimes found in the blood of leukæmia.

(5) *Marrow cells* are for the most part very large cells, whose nuclei are very poor in chromatin, and almost fill up the entire cell. They arise in the bone marrow (Cornil, Müller). Sometimes they may be eosinophilic (see leukæmia, below).

Neusser (22) has recently described what he considers a new discovery with regard to the leucocytes. In using his modified Ehrlich mixture he found that certain of the leucocytes in blood-films taken from patients suffering from the uric acid diathesis showed granules and small masses in the protoplasmic zone, deeply stained with the basic dye. Neusser thinks these substances, which are chiefly found in the mononuclear cells, consist of matter allied to nucleoalbumin, and he considers them to be a sign of increased production of uric acid. They are found in some cases of chronic phthisis, and Neusser thinks this a favourable sign, as they indicate the uric acid diathesis. They are said to appear also in diabetes and myelogenous leukæmia. Pascheles investigated this matter in my laboratories, and found that these granules would appear and disappear in the blood of different diseases for weeks at a time, and that therefore they indicated no diathesis at all. Löwit found them normally in rabbits, and recently Janowski ('Arch. f. exp. Path.,' Bd. xxxvi) has described the same appearances in pus cells, and considers them to be products of degeneration; and this, no doubt, is the rational explanation.

The total number of leucocytes in the circulation is very variable, and depends on widely different factors. Nevertheless we have certain estimates of the number normally present in healthy persons. Thoma (23) estimated this as 6784—10,590 per c.mm.; Boeckmann (24) and Halla (25), 4960—10,106; Tumas (26), 4800—9600; Graeber (27) and Reinecke (28), 7134—7351. Personally (29) I think the normal number in moderately well-nourished individuals, who have neither fasted for long nor are in the middle of digestion, is 8000—9000, and that variations of 1000 either way may be considered as normal.

The number of leucocytes in the circulation is affected by widely different circumstances. Vaso-motor action and variations in the volume of plasma may cause an increase or decrease. Further, the number varies in different parts of the system under physiological conditions, and this variation may be intensified in pathological conditions. Again, the leucocytes differ from the red corpuscles in that certain influences cause them to enter or leave the circulation in greater or smaller numbers (chemiotaxis). The former condition is called leucocytosis or hyperleucocytosis, and where possible we add an adjective indicating the ætiology, *e.g.* inflammatory or digestive leucocytosis; for the latter condition Löwit proposes the name of leucopænia. Leucocytosis is, then, an increase in the number of leucocytes in the circulation; this is usually transitory, chiefly affects the polymorphonuclear neutrophile forms, and is brought about by the most widely different causes. Opinions have of late been at variance with regard to the theory of the formation of leucocytosis, but a series of investigations recently published by Goldscheider and Jakob (30) appears to offer a satisfactory explanation. The fact that a transitory leucocytosis is caused by food, by medicaments, and by the influence of an acute infection has long been known. I, however, was the first to point out that the various forms of leucocytosis depended upon chemiotactic action. My clinical and experimental observations had suggested an intimate connection between inflammatory leucocytosis and the formation of exudation. This assumption has stood the test of experience for the majority of cases, at any rate, though it is true that leucocytosis may exist without exudation. I suggested that the leucocytosis was in proportion to the amount and quality of the virus introduced. When we deal with pyogenic organisms or their products, the amount of exudation, as well as that of leucocytosis, depends on the degree of their virulence. The increased number of leucocytes driven into the circulation were, according to my view, attracted out of the organs into the vessels by the unexplained chemiotactic action of the products of the micro-organism, or other substances, and in part appeared as exudations at the site of the established inflammation. This view was first contested by Joas (31) and later by Löwit (32). These authors considered that leucocytosis was a sign of regeneration, and discarded chemiotactic action; for they discovered, what I had failed to perceive, that the increase of leucocytes was preceded by a diminution. They showed that injections of bacterial proteins, hemialbumose, peptone, nucleic acid, first caused a diminution of leucocytes, and suggested that this was due to the destruction of these cells (leucolysis). Römer (33) and Buchner (34), again, look at the question from a different point of view. They hold that the micro-organisms directly stimulate the leucocytes, not by means of their products, as I assumed, but by the proteins which they contain, as soon as these are dissolved in the tissue fluids. They say the number is not increased by cells passing out of the organs, but by amitotic division. We see, then, that there were many theories, and that there was agreement only on one point, viz. that certain substances incorporated in the body caused an increase of leucocytes in the blood. Even this has been denied by Schultz (33) on the ground of certain experiments he made on rabbits; he holds that there is no absolute increase or diminution in the number of leucocytes, and that any apparent increase or decrease is wholly due to the unequal distribution of the white cells in the circulation. The theories have recently undergone a searching examination by Goldscheider and Jakob. The results found previously were partly confirmed and partly corrected, and a new theory of leucocytosis and hypoleucocytosis built up, which is largely based on chemiotaxis. These authors found that the initial diminution of leucocytes, after injection of hemialbumose, etc., observed by Löwit, occurred in the majority, but not in all of their cases. They showed, however, that a destruction of leucocytes (leucopænia), if it occurred at all, played only a subsidiary part, for at this stage a considerable increase of leucocytes, especially the polynuclear form, appeared in the capillaries and smallest vessels of certain organs, more especially the lungs. Schultz's observation that Löwit's leucopænia did not occur, and that the appearance he noted was due to an increase of the leucocytes in the internal organs, was correct. His other conclusion that leucocytosis also did not occur, but was merely simulated on account of a diminution of leucocytes in the internal organs, was not correct, for the authors found leucocytosis existing simultaneously in the superficial and internal vessels. Goldscheider and Jakob do not recognise the connection I made between exudation and leucocytosis, for they often found leucocytosis without any exudation. When I made the statement, however, it seemed a probable one at the time, and even now holds good clinically for the majority of cases. With regard to the origin of the increased number of leucocytes, Goldscheider and Jakob agree with me in attributing it to their attraction out of the blood-forming organs, and they oppose Römer's view of an intra-vascular formation of new leucocytes. They attribute this puzzling sudden appearance of numerous leucocytes, as do a large number of other authors (36—40), to chemiotaxis, and are inclined to accept Hertwig's (40) explanation of this phenomenon. It has been found by many (41—45) that certain products of micro-organisms will produce aseptic suppuration at the place of injection. Leber has produced a crystalline substance from cultures of staphylococci which has the same effect, viz. phlogosin. Leber also drew an analogy between this chemiotactic action and the action of certain substances on the spermatoids of the cryptogams, which had been previously demonstrated by Pfeiffer and Stahl, the botanists.

The mystery of the action of chemiotaxis has not yet been fathomed, but our knowledge has increased a little, and we know that there are substances which have a negative chemiotactic action as well as those which have a positive chemiotactic action on the leucocytes. Hertwig has finally proposed a theory of the production of the condition which Goldscheider and Jakob accept :

"These substances attract or repel the leucocytes according to their percentage in the fluid which reaches the tissues. The repellent action of any substance is very small when there are only small amounts of it in the circulation. The attractive action gradually increases if these small doses are repeated at intervals; every single injection causes a certain stimulation of the blood-making organs, and so we obtain a considerable leucocytosis. If we inject a moderately strong dose, the first thing we notice is the repellent action on the leucocytes, which crowd into the capillaries and remain there. The injected substance gradually becomes diffused, and loses its high degree of concentration and therefore its repellent effect, so that it now stimulates the blood-forming organs to expel the leucocytes they contain, and also to manufacture new leucocytes. The third case is that in which we inject an excessive dose. Here the repellent effect must be at first very great. On the other hand, so large a quantity of substance in the circulation must soon exercise its power on the blood-forming organs. At first the new cells are repelled and crowded in the capillaries, but soon the action on the organs is so powerful that in a relatively short time leucocytosis obtains."

At the present day we have not got a thorough insight into the actions of positive and negative chemiotaxis, and are limited to the knowledge of a few facts, but Goldscheider and Jakob deserve the credit of having sifted and increased the number of these.

We can get leucocytosis from a large number of different causes, as the number of chemiotactic substances is very large. We may classify the various forms as follows:

A. *Physiological leucocytosis*:
  (*a*) Digestive leucocytosis.
  (*b*) Leucocytosis of pregnancy.
  (*c*) Leucocytosis of the new-born.
B. *Pathological leucocytosis*:
  (*a*) Inflammatory leucocytosis.
  (*b*) Malignant leucocytosis.
  (*c*) Post-hæmorrhagic leucocytosis.
  (*d*) Pre-mortal, or the leucocytosis of the agony.

C. *Leucocytosis due to therapeutic and other influences.*

A. PHYSIOLOGICAL LEUCOCYTOSIS.

(*a*) *Digestive leucocytosis.*—The existence of a digestive leucocytosis, which has been asserted by some (46—48) and denied by others (49—53), was proved by Pohl's (54) investigations in dogs. I showed that it occurred in man. Two examples will suffice.

CASE I.

Time.	Number of leucocytes.	Observations.
11.15 a.m.	7,600	Had fasted 18 hours, meal at 11.15.
12.15 p.m.	6,000	
1.15 ,,	8,500	
3.15 ,,	12,000	
5.15 ,,	14,000	
7.15 ,,	10,000	

CASE II.

11.30 a.m.	5,800	Had fasted 18 hours, meal at 11.15.
12.30 p.m.	10,600	
1.30 ,,	10,600	
2.30 ,,	9,600	
3.30 ,,	6,800	
6.0 ,,	6,600	

We see that ingestion of food is followed by an increase of leucocytes. Sometimes, however, we find an absence of digestive leucocytosis in healthy persons. This occurs also under pathological conditions, especially in the different forms of anæmia, or in those suffering from affections of the gastro-intestinal canal. Possibly sluggishness of the bowels is the cause of this in normal cases. In spite of this exception, we can state as a general rule, that a transitory leucocytosis occurs after food (especially if there has been a previous abstinence), and that albumens produce more marked results than other food (Pohl, Reinert [56], and Rieder). Children show a relatively greater amount of leucocytosis than adults (57, 58). Abstinence from food has the contrary effect, but this is not so pronounced. Luciani (59) examined the blood of the fasting man, Succi, and found the number of leucocytes decreased from 14,530 to 861 during the first seven days of fast. On the eighth day it was 1530, and it remained at this level to the end of his thirty-day fast. I examined the blood of a lunatic who had refused food for eight days, and found the number of leucocytes to be 2800. These facts fit in well with the theory that the presence or absence of chemiotactic substances in the food affects the number of leucocytes, and is supported by the common experience that well-nourished individuals have a greater number of leucocytes on an average than debilitated people, even if the latter are free from disease (*e. g.* I found in a strong, well-nourished student, twenty-eight years old, 12,000 before a meal, and three hours after 14,000; in a badly nourished old woman, age seventy-two, a beggar, with no organic disease, 3000 before and 5400 after a meal).

This is a fact that should be taken into account in estimating the number of leucocytes of a patient; *e. g.* in a strong man we cannot consider 10,000 leucocytes as leucocytosis, whereas in a debilitated individual we should consider this number as a pathological increase. R. Müller and later Schneyer (60) have attempted to use the appearance of leucocytosis as a basis for estimating the time at which absorption of food takes place. Müller, with this view, examined cases of anæmia, chlorosis, carcinoma of stomach, with and without free hydrochloric acid in the gastric secretion, and conditions of obstruction in the region of the inferior vena cava. He came to the conclusion that severe damage to the constitution of the blood, and even passive hyperæmia of the abdominal organs, did not delay the appearance of digestive leucocytosis, but that in cases of carcinoma of the stomach (independently of the existence of free hydrochloric acid) no leucocytosis occurred even after the most ample meal. This absence of leucocytosis in gastric cancer was confirmed by Schneyer, who showed that it was not due to pyloric stenosis, for patients with well-marked pyloric stenosis invariably showed distinct leucocytosis after meals. In cases of gastric ulcer, digestive leucocytosis appears as usual. Schneyer thinks the absence of leucocytosis in malignant disease of the stomach is due partly to a simultaneous catarrh of the gastric mucous membrane, and partly to the fact that the lymphatic system is affected. Whatever the cause, the examination of the number of leucocytes in gastric cases may be said to be of clinical and diagnostic importance, since the existence of digestive leucocytosis would seem to contra-indicate carcinoma.

(*b*) *Leucocytosis of pregnancy.*—Moleschott and Nasse (61) were the first to demonstrate an increase of leucocytes in pregnancy. Halla found a moderately large amount of leucocytosis in some cases, but in others none. My own observations show similar results. In four healthy pregnant women I found one had 11,000—13,000 leucocytes; the others 5000—8000, *i. e.* the normal amount. Rieder examined thirty-one cases after fourteen to sixteen hours' fast, and found that twenty-one had a distinct leucocytosis of, on the average, 13,000. He failed to find leucocytosis only in multiparæ (in eight out of seventeen cases). A valid explanation of this form of leucocytosis has not yet been given. Virchow (62) attributed it to an increase of the lymphatic glands and vessels about the uterus. Whether this really has any influence is hard to say, but it is certain that enlargement of the lymph-glands does not necessarily cause leucocytosis. As far as my experience goes, my opinion is that the fact that leucocytosis is not invariable in pregnancy, shows that pregnancy in itself does not cause leucocytosis, but that the leucocytosis which usually occurs must be due to concomitant circumstances (*e. g.* an abnormally strong or protracted digestive leucocytosis, or perhaps the swelling of the mammæ, which in these cases may be seen, microscopically, to be full of round-cells).

Confinement seems to have an effect on the number of leucocytes, for it is followed soon afterwards by a fall in the leucocytosis. Rieder has given examples of this. Mallassez (63) found that an increase of leucocytes occurred directly after confinement, and that in normal cases this gradually disappeared. This is perhaps comparable with the leucocytosis which follows loss of blood. I do not know of any investigation as to the question whether *lactation* has any effect or not, but in lactation there are many influences at work—especially increased taking of nourishment—which by themselves could cause an increased number of leucocytes. The influence of *menstruation* on the number of leucocytes is that of greater or smaller loss of blood.

(*c*) *Leucocytosis of the new-born.*—In the very first days of life there is a relatively large number of leucocytes in the blood, but otherwise, I think, neither age nor sex has a direct influence on the number of these cells. Schiff divides the early days of life into two parts according to the relations of the leucocytes. In the first period there is an increase in their number, in the second a relative diminution.

This primary leucocytosis must be attributed in part to the concentration of the blood analogous to the polycythæmia of the new-born (Cohnstein and Zuntz, 64), and in part to a protracted digestive leucocytosis. Rieder has drawn attention to the fact that the leucocytosis of the new-born differs from other leucocytoses in the fact that the majority of the cells are not polynuclear cells, but lymphocytes.

Example of the number of leucocytes in mother and child :

Mother.		*Child.*	
May 27th . .	17,900	Born May 28th.	
Confinement.		12 hours after birth	19,100
,, 28th, Morning	13,400	May 29th . .	14,900
,, ,, Evening	13,200	,, 31st . .	9,100
,, 31st . .	10,000	June 3rd . .	12,200
June 3rd . .	8,800		

B. PATHOLOGICAL LEUCOCYTOSIS.

(*a*) *Inflammatory leucocytosis and the relations of the leucocytes in acute infectious diseases.*—By inflammatory leucocytosis we mean that transitory increase of the neutrophile polynuclear cells which accompanies many acute infectious diseases, more especially during the febrile stage. Different diseases show differences in the relations of the number of leucocytes. It is important, in forming a judgment from the number of these cells, to first make an assumption—on the lines mentioned above—as to what should be the normal number in the person in question, taking into account the influence of the condition of nutrition upon the number of leucocytes.

In acute diseases the inflammatory leucocytosis often, but not always, declines with the fever; sometimes it outlasts the fever for a short time, sometimes falls before it. This is probably due to the products of micro-organisms, which act chemiotactically on the leucocytes. Buchner (65) erroneously assumed that the proteins in the bodies of the organisms, and not the toxin, were the cause of this chemiotaxis. Ancient writings teem with observations of the *crusta phlogistica* and hæmitis (Piorry, 66), but investigations of the numerical relations of the leucocytes in acute infectious diseases are few in number up to the time of Virchow (67). Boechmann (68), Halla, Tumas (69), and v. Jaksch (70) arrived at the conclusion that there was a connection between the height of the temperature and the number of leucocytes and red corpuscles. Boechmann, in fact, said—what is undoubtedly not true—that the number of red corpuscles was indirectly, and the number of leucocytes directly, proportional to the height of the temperature. My own observations (loc. cit.), and later those of G. Pick (71) and of Pée (72), have increased the clinical literature of this subject and added to our knowledge.

As the relations of the leucocytes in infectious diseases in general are somewhat complicated, we will consider the diseases separately.

(i) *Croupous pneumonia.*—Halla, Hayem, and Gilbert (73) formerly observed that the majority of cases of pneumonia were accompanied by an inflammatory leucocytosis. Later observers (74—80) have confirmed this, and pneumonia is now in this respect the best known of all the infectious fevers. In the majority of cases there is an increase of the polynuclear leucocytes during the febrile stage, which in general runs parallel to the temperature curve.

Example I.—B. W—, æt. 27, smith. Hitherto healthy, but seized with rigor, high fever, and pain in right side of chest. Admitted into hospital January 22nd.

Date.	Temp. Morning.	Temp. Evening.	No. of leucocytes.
Jan. 22	—	40·2° C.	14,000
,, 23	39·4° C.	40·0	14,000
,, 24	39·6	40·3	18,000
,, 25	36·4	38·8	18,000
,, 26	38·0	38·4	24,000
,, 27	38·0	38·9	22,000
,, 28	37·2	38·1	23,000
,, 29	37·6	38·1	12,000
,, 30	37·4	38·8	10,000
,, 31	37·2	37·3	9,000

The parallelism between the number of leucocytes and the temperature is not always so marked. Sometimes the latter, but more often the former, falls first.

Example II.—K. M—, æt. 25, cook. Taken ill with double pneumonia June 7th. Admitted June 12th.

Date.	Temp. Morning.	Temp. Evening.	No. of leucocytes.
June 12	38·8° C.	39·0° C.	23,000
,, 13	38·4	40·3	20,000
,, 14	39·6	39·2	19,000
,, 15	39·5	37·2	8,000
,, 16	37·0	36·4	11,000
,, 17	36·6	37·0	10,000

Example III.—K. J—, æt. 21, tailor. Taken ill May 7th. Came under observation May 11th.

Date.	Temp. Morning.	Temp. Evening.	No. of leucocytes.
May 11	38·4° C.	40·6° C.	17,000
,, 12	39·6	39·6	17,000
,, 13	39·0	39·3	20,000
,, 14	38·8	39·2	20,000
,, 15	38·6	39·4	25,000
,, 16	37·4	37·8	21,000
,, 17	37·2	37·4	9,000

The leucocytosis does not fall in the so-called pseudo-crises, although the temperature falls, but may even increase; in fatal issues an increase in the number of leucocytes often occurs towards the end. The majority of cases show leucocytosis, but there are instances in which it is altogether absent. In these cases the prognosis is said to be bad.

Tschistovitch (77) has made valuable observations in this respect. He showed that inoculation with Fränkel's diplococcus in rabbits caused a leucocytosis, the intensity of which varied with the virulence of the culture. If highly virulent cocci were used, there was not only no leucocytosis, but, on the contrary, a diminution of leucocytes ensued, and the animals died. These results were confirmed later by Rieder (73), and seem to be of importance for the comprehension of the appearance or absence of leucocytosis, not only in pneumonia, but also in other diseases. v. Jaksch suggested that substances which caused this increase of white cells should be injected into the blood as a therapeutic measure in those cases of pneumonia in which there is leucocytosis. To determine the effect of this, Tschistovitch injected cultures of *Staphylococcus aureus* (which always cause an increase of leucocytes), together with very virulent diplococci, into rabbits. The result was a surprise, as the staphylococci caused no reaction, and no leucocytosis appeared. Dogs, which resist the diplococci much better than rabbits, survive experimental inoculation of these micro-organisms more easily, but show at the same time very little leucocytosis. It follows, then, that the appearance or non-appearance of leucocytosis in pneumonia does not afford a certain prognostic sign, and that it is dependent on the relations of the virulence of the injected material to the resistance of the organism. Hence we come across cases with a fatal termination, in some of which there is no leucocytosis, whilst others have shown a distinct increase in the number of white cells (Maragliano).

The amount of leucocytosis has no relation to the amount of exudation in the lungs. The latter depends on the virulence of the infection, and also on the condition of the body; thus we often see debilitated cases with a large amount of exudation, and well-nourished individuals with relatively small amounts.

(ii) *Non-tubercular inflammations of the serous membranes.*—Here, also, the appearance of leucocytosis depends in the first instance on the condition of the infecting material. As this influences the quality of the exudation, we get a certain parallelism between the richness of the exudation in cells and the amount of the leucocytosis. Tubercular affections of these membranes form an exception.

Inflammations of the pleura in which we have the formation of sero-fibrinous or tubercular exudation are accompanied, in general, by a moderate increase.

Example I. — P. M—, æt. 40, servant. Right-sided sero-fibrinous pleurisy. Entered hospital 1st March.

From March 1st to 6th the temperature varied between 39° and 40°; the number of red cells on March 2nd was 4,290,000. This sank to 3,860,000 by March 5th, and then rose again shortly before the rise of temperature to 4,110,000. The number of leucocytes varied from 13,000 to 15,000. On March 7th the temperature fell to normal, when the number of leucocytes then rose to 16,000. On March 8th the temperature rose to 38·8°, and was remittent in type late in March; the number of white cells during this period varied below 18,000 and 19,000 and then fell slowly to normal, to 13,000 on March 14th, and 8000 on March 20th. Purulent inflammation usually shows higher values.

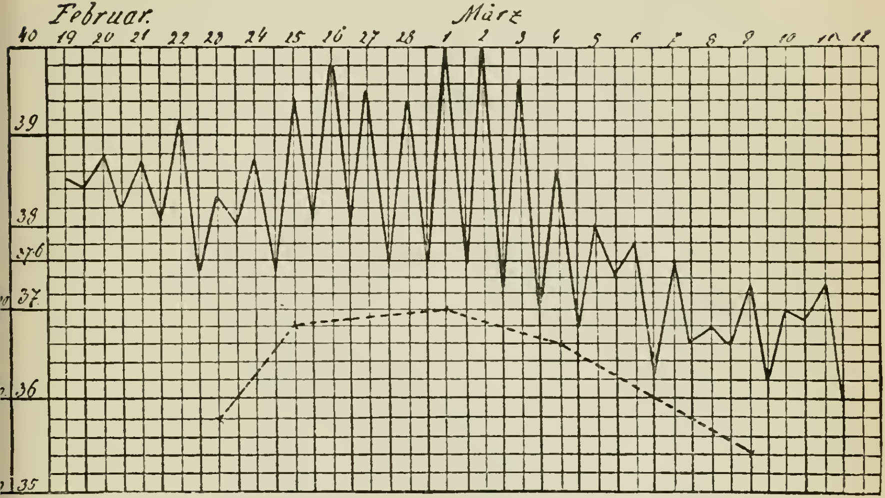
Example II.—K. A—, æt. 23, servant. Purulent meningitis. Admitted into hospital 11th February; died February 25th.

Date.	Temp. Morning.	Temp. Evening.	No. of red cells.	No. of leucocytes.
Feb. 12	40·0° C.	41·5° C.	5,100,000	22,000
,, 13	39·0	41·0	—	21,000
,, 14	38·7	40·0	4,980,000	14,000
,, 15	41·4	—	—	15,000

In gonorrhœal peritonitis there is usually leucocytosis. As seems to be the rule for all diseases of serous membranes, this sign exists only at the same time as the fever. If the exudation has become stationary, the leucocytosis disappears, sometimes completely, but if the fever recurs, it returns. So we see often, and I have especially noticed this in gonorrhœal para- and perimetritis, a certain parallelism between the number of leucocytes and the average temperature.

Example III.—F. H—, maid. Gonorrhœa with parametritis. The dotted line represents the number of leucocytes.

FIG. 20.



Rieder's results were similar, and agree with mine as to the value of leucocytosis in the differential diagnosis between tubercular and non-tubercular affections of the serous membranes.

(iii) *Septicæmia.*—The cases that fall under this heading vary in character. They always involve organisms which can cause suppuration. Nevertheless some cases show no leucocytosis, and some a very large amount.

Example I.—K. K—, æt. 24. Confined fourteen days before she came under observation. Rigor eleven days after confinement. Septic diarrhœa. Died in six days.

Post-mortem :—Septic endometritis.

Date.		Temp. Morning.		Temp. Evening.		No. of leucocytes.
July 4	...	39·2° C.	...	40·2° C.	...	—
„ 5	...	39·8	...	41·3	...	3000
„ 6	...	40·4	...	41·3	...	6000
„ 7	...	40·6	...	41·6	...	5000
„ 8	...	40·6	...	40·6	...	4000
„ 9	...	39·5	...	40·6	...	—
„ 10	...	—	...	40·8	...	Died.

Example II.—A. S—, æt. 21. Septicæmia. Malignant endocarditis; acute rheumatism (see Rieder, loc. cit., p. 129, No. 1). Frequent rigors; severe rigor, January 11th.

Date.		Temp.		No. of leucocytes.
Jan. 2	...	41·0° C.	...	17,000
„ 3	...	37·7	...	13,700
„ 8	...	39·3	...	15,500
„ 10	...	38·8	...	18,000
„ 12	...	38·8	...	21,300

Rieder found leucocytosis in all his cases, and therefore contests my results. I think the explanation of our differences may lie in the discoveries of Tschistovitch mentioned above. It seems possible, by analogy, that highly virulent staphylococci and streptococci may cause no leucocytosis in man, and bring about a fatal result. We may perhaps go further, and say, that when the leucocytosis does occur it is a sign of the relative weakening of the virulence of the organism towards the body affected. The well-known fact that the power certain bacilli have of producing suppuration is dependent on a degree of virulence which must lie between certain limits, is in favour of this, *e. g.* the typhoid bacillus only excites suppuration when its virulence has been weakened. Suppuration and leucocytosis are therefore comparable, in that both are functions of the relative relations of the degree of virulence of the injected matter and of the resistance of the infected body. Clinical experience, too, shows that there is a certain connection between the formation of exudation and the leucocytosis, although it is true that substances exist which cause leucocytosis without any exudation, and more rarely that cases occur of exudation without leucocytosis. Innumerable observations at the bedside have led me to the following conclusions: that (apart from leucocytosis caused by drugs or other influences, *e. g.* loss of blood)—(1) The existence of leucocytosis in a patient implies that an exudation is forming in the body. (2) A high degree of leucocytosis means an exudation rich in cells, *i. e.* pus, and a small degree means serous exudation. (3) Absence of leucocytosis, if it does not exclude, makes the existence of an exudation improbable, unless the disease is tubercular.

Certain other diseases which we have not yet discussed show this dependence of leucocytosis upon exudation, *e. g.* acute rheumatism, tonsillitis, diphtheria, variola, measles, typhoid, malaria, and tuberculosis. Others do not follow the above rule, *e. g.* erysipelas, scarlatina, and tetanus. Examples of these diseases will now be given.

(iv) *Acute rheumatism.*—Rieder and I have found, as a rule, moderate leucocytosis.

O. J—, æt. 51. Became ill May 28th. Admitted June 1st.

Date.	Temp. Morning.	Temp. Evening.	No. of leucocytes.
June 3	—	39·0° C.	6,000
,, 4	38·8° C.	39·2	10,000
,, 5	38·6	39·0	11,000
,, 6	37·6	38·0	8,000
,, 7	37·4	38·6	8,000
,, 8	37·4	37·5	—
,, 9	37·2	37·4	6,000
,, 10	37·0	37·2	—
,, 11	36·8	37·2	6,000

(v) *Diphtheria.*—Moderate leucocytosis is found, which declines on abatement of the fever.

Example (rom Pée).—Servant maid, æt. 18. Admitted 26th March.

Date.	Temp.	No. of leucocytes.
March 26	38·9° C.	16,000
,, 27	37·2	14,000
,, 28	37·9	11,000
,, 29	37·4	7,000
,, 31	37·0	7,000

In *tonsillitis,* too, Halla has noted increase of leucocytes during the febrile stage.

(vi) *Variola.*—In addition to the few cases given by Halla and Brouardel (81), we have the comprehensive investigations of R. Pick (82), who examined forty-two cases of various degrees of severity. *Very mild* cases showed no leucocytosis.

Example.—A. V—, æt. 22. Vaccinated.

Date.	Day of disease.	Temp. Morn.	Temp. Even.	No. of leucocytes.
Dec. 14	3	—	40·4° C.	4200
„ 15	4	38·6° C.	38·7	3350
„ 16	5	37·4	37·4	3600

MORE SEVERE CASES (*Variola modificata*).

At the beginning there is no leucocytosis if there are no complications. As suppuration begins in the pustules, the number of leucocytes increases and then slowly declines.

Example.—J. Z—, æt. 34. Vaccinated.

Date.	Day of disease.	No. of leucocytes.	Temperature.		Observations.
			Morning.	Evening.	
Oct. 17	5	4.200	...	40·0	
„ 18	6	6,600	38·6	37·0	Eruption increased.
„ 19	7	8,000	37·0	37·4	Opacity of vesicles.
„ 20	8	11,600	37·2	37·3	Suppuration beginning.
„ 21	9	11,000	36·8	37·4	Suppuration general.
„ 22	10	17,200	37·6	38·0	Pustules mature and distended.
„ 23	11	14.300	37·0	38·0	Beginning to dry up.
„ 24	12	9.600	37·8	38·0	Drying up and scabbing.
„ 25	13	7.600	37·0	37·2	
„ 26	14	9.700	37·2	36·8	Convalescence.

The influence of suppuration is seen to be well marked. Pick's cases of variola vera showed the same results, but the suppuration and leucocytosis lasted longer; further, the leucocytosis in this case also did not begin before the suppuration. Pick therefore comes to the following conclusions:—"The infection of smallpox in itself causes no leucocytosis, for we find no leucocytosis in the stage of eruption during the highest fever and in the severest cases. The secondary infection with pyogenic micro-organisms causes moderate leucocytosis, which is generally proportional to the severity of the case; if the case ends fatally, leucocytosis is absent."

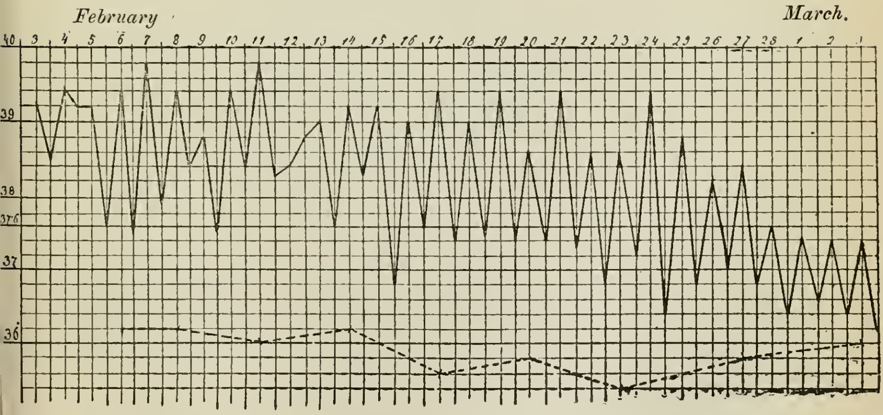
Satisfactory as Pick's results are with regard to my own statements as to the connection of suppuration and leucocytosis, this secondary pyogenic infection in smallpox that he and the majority of pathologists assume does not seem to me to be sufficiently proved. In any case the possibility that the suppuration and leucocytosis indicate weakening of the virus should be borne in mind.

(vii) *Measles.—Example* (Pée).—S—, æt. 27. Uncomplicated measles show no leucocytosis.

Date		Temp.		No. of leucocytes.
April 3	...	39·3° C.	...	4000
„ 4	...	37·0	...	5000
„ 5	...	37·2	...	7000
„ 6	...	37·5	...	6000
„ 8	...	37·1	...	8000

(viii) *Enteric fever.*—Virchow stated that leucocytosis existed in this disease. Later, Halla found that it existed in moderate degree only in isolated cases, whilst Tumas found normal numbers of leucocytes during the whole course of the disease. In my observations on the subject I have shown that there is no leucocytosis, but, on the contrary, often a diminution of leucocytes. Leucocytosis occurs only if complications exist, *e. g.* suppuration or pneumonia; but even in these cases it is often absent. The analogy with Tschistovitch's experiments is striking.

FIG. 21.



Examples.

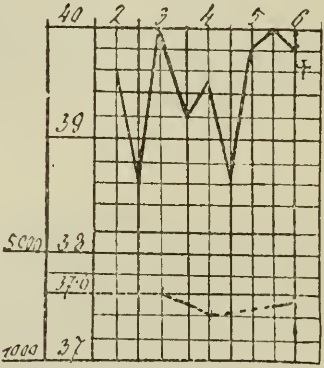
CASE I.—J. K—, æt. 29. On February 6th a phlegmonous inflammation of the plantar fascia developed; this was incised

February 9th, when one third of a litre of pus was evacuated. On the 11th February a small abscess in the finger was opened. On March 1st solid food was given. The dotted line represents the number of leucocytes. We see that the number of leucocytes is below the normal, and that no leucocytosis occurred in spite of the suppuration. Other causes, too, which generally cause leucocytosis seem to fail to do so in this disease, as *e. g.* loss of blood and catarrhal pneumonia, as in the two following cases :

Case 2.—P. R—, æt. 20, painter. December 2nd, delirious. Abundant roseola on chest and abdomen. Spleen palpable. Picking at bedclothes. Subsultus tendinum. Diarrhœa; stools evacuated into bed. Bedsore. On December 5th hæmorrhage from bowels. Died December 6th.

Fig. 22.

December.

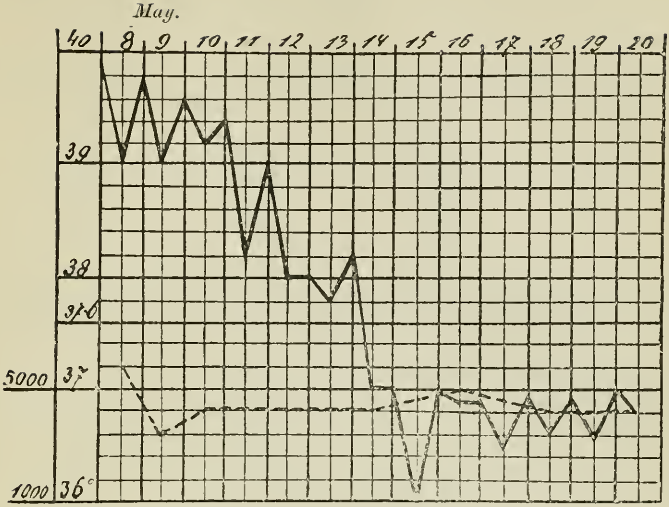


Case 3.—A. H—, æt. 24, housemaid. May 8th admitted. On 9th rusty sputum, no dulness, harsh breathing on right side of chest. 12th, sputum muco-purulent and slightly blood-stained. Râles over right lung.

(ix) *Typhus fever,* absence of leucocytosis.

Example.—Painter, æt. 23 (from Tumas, l. c., p. 263).

FIG. 23.



Date.	Day of disease.	Temperature.		Weight.	Number of red cells per mm.^{3}	Hæmoglobin in %. [Malassez.]	No. of white cells.	Proportion of white to red.	Remarks.
		Morn.	Even.						
Jan.									
4	4	—	40·0°	—	—	—	—	—	Fluid stools, albumen in urine in considerable quantity.
5	5	39·2°	39·6	50·700	4,440,000	11	9600	1 : 443	
6	6	39·0	39·5	50·600	4.220,000	$10\frac{1}{2}$	4800	1 : 442	
7	7	39·0	40·0	49·450	—	—	—	—	Pulse feeble.
8	8	39·2	39·3	—	4,280,000	$10\frac{1}{2}$	3200	1 : 854	
9	9	39·0	39·5	48·500	—	—	—	—	Condition worse. stools fluid.
10	10	38·8	39·2	—	4,440,000	$10\frac{1}{2}$	3200	1 : 889	
11	11	38·3	39·3	47·250	—	—	—	—	Patient asleep, number of secondary petechiæ, pulse weak.
12	12	39·0	39·2	—	4,380,000	11	1600	1 : 876	
13	13	38·8	39·5	46·860	4,780,000	11	3200	1 : 895	
14	14	38·7	39·0	—	—	—	—	—	
15	15	38·0	38·7	45·450	4,960,000	11	1600	1 : 987	
16	16	38·1	38·8	—	—	—	—	—	Condition better.
17	17	38·7	38·6	—	4,160,000	$9\frac{5}{8}$	4800	1 : 832	
18	18	37·7	38·2	43·000	—	—	—	—	
19	19	36·6	38·5	—	3,820,000	$9\frac{3}{8}$	1600	1 : 623	Condition worse.
20	20	38·1	38·3	—	—	—	—	—	Night sweats; condition worse; stools (2–3) fluid.
21	21	37·5	38·1	—	3,450,000	$8\frac{3}{4}$	3280	1 : 690	
22	22	38·1	37·8	41·000	3.450,000	$8\frac{1}{2}$	3200	1 : 420	
23	23	37·5	38·0	41·250	—	—	—	—	Tonsil gangrenous.
24	24	37·4	38·0	41·850	3,130,000	7	3200	1 : 312	
25	25	37·4	39·3	41·500	—	—	—	—	Patient becomes weaker and dies.
26	26	39·2	—	41·250	—	—	—	—	

(x) *Malaria.*—In the typical tertian and quartan form there is no leucocytosis. (With regard to the other forms, see below.)

Example.—Br. A—, moderate fever of tertian type; parasite observed.

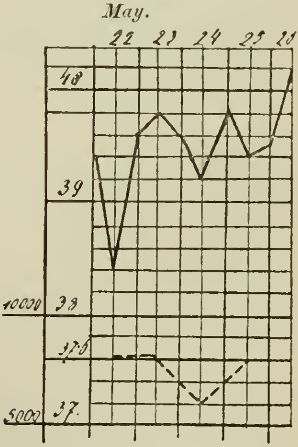
Date.		Temp. Morning.		Temp. Evening.		White cells.
May 14	...	37·2° C.	...	36·4° C.	...	4000
„ 15	...	37·4	...	39·0	...	3000
„ 16	...	36·8	...	36·6	...	4500
„ 17	...	37·3	...	37·2	...	4000

(xi) *Tuberculosis.*—Purely tubercular infection in itself causes no leucocytosis. We find that even at the time of high fever, the number of leucocytes is not at all increased in tubercular meningitis and peritonitis.

Example.—W. D—, æt. 23, shoemaker. May 22nd, left facial paralysis, abundant suppuration from left ear, rigidity of neck, retracted abdomen, etc. 26th, died.

Post-mortem.—Tuberculous meningitis.

Fig. 24.



The absence of leucocytosis is of importance in the differential diagnosis of tubercular inflammation of the serous membranes from septic inflammations. The existence of a leucocytosis in meningitis, however, does not indicate that it is of a septic nature unless all other causes of leucocytosis are excluded. The number of leucocytes in acute miliary tubercle of the lungs is similar to what is found in tuberculous inflammations of the serous membranes; there is an absence of leucocytosis. This is an important fact in the differential diagnosis of this disease from acute bronchitis or typhoid fever, as acute bronchitis is always accompanied by leucocytosis (generally about 15,000), whilst typhoid fever shows a diminution of leucocytes and acute miliary tubercle gives normal values, generally between 7000 and 10,000. Although the acute tubercular diseases are always unaccompanied by a leucocytosis, we find that in the chronic tuberculous affections, especially phthisis, other influences are at work which affect the number of leucocytes: thus, apart from hæmorrhage, sweating, and diarrhœa, we have to consider the effect of various pyogenic bacilli. Cases of commencing phthisis show no increase of leucocytes, whereas cases which have reached the stage of excavation are invariably accompanied by leucocytosis. A moderate increase of leucocytes results if hæmoptysis occurs, as is the case after any loss of blood.

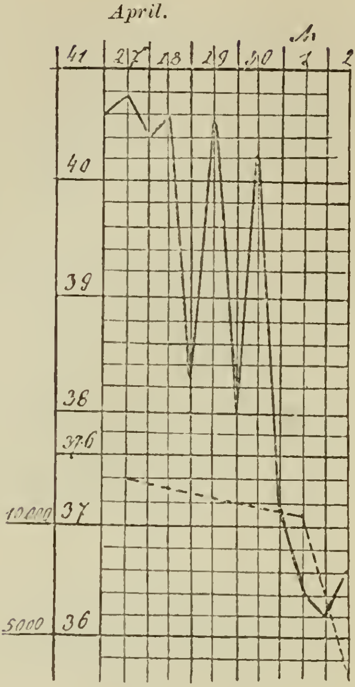
Tuberculosis of the intestines is generally accompanied by a moderate leucocytosis, especially in fatal cases. These facts are obviously valuable from a diagnostic point of view. The infiltrated form of tubercle of the lungs differs from the above in that the numbers we obtain appear to differ according to the individual case. Thus we see cases with normal numbers of leucocytes, and some with large amounts of leucocytosis, resembling croupous pneumonia so closely that an examination of the blood alone would not enable us to distinguish between the two diseases. Injections of tuberculin in a tubercular patient cause leucocytosis, and at the same time an increase of the eosinophile cells (Bischoff).

(xii) *Erysipelas.*—This is accompanied by a leucocytosis which is usually moderate.

Example.—A. M—, æt. 32.

The leucocytosis often declines about the same time as, sometimes before, the temperature. In the latter case we can prognosticate the approaching decline of the fever.

FIG. 25.



(xiii) *Scarlatina* differs from the diseases so far discussed. Thus, whereas in pneumonia and erysipelas the leucocytosis rarely outlasts the fever for any length of time, but as a rule disappears when the temperature becomes normal, it seems to be a characteristic of scarlatina that the leucocytosis persists long after all signs of the disease have disappeared. Rieder says, "We may conclude that the number of leucocytes does not become normal until all the toxic matter in the blood has been eliminated. In this way it is perhaps possible to form an opinion as to whether scarlatinal nephritis is likely to ensue or not." Rieder, however, did not examine his cases for a sufficiently long period of time to confirm this idea.

I give a case of my own which was examined for three weeks.

Example.—F. G—, æt. 14. Well-marked rash. Slight bronchitis. No albuminuria throughout.

Date.	Temp. Morning.	Temp. Evening.	No. of leucocytes.
Feb. 1	—	40·4° C.	30,000
„ 2	38·6° C.	38·4	22,000
„ 3	37·6	37·4	27,000
„ 4	37·0	37·4	16,500
„ 5	37·0	37·0	17,500
„ 6	36·8	37·1	16,500
„ 7	36·4	36·8	12,800
„ 8	36·8	36·8	15,500
„ 9	36·6	36·6	15,000
„ 10	36·5	36·7	14,000
„ 11	36·6	36·5	13,000
„ 12	36·5	36·1	15,800
„ 13	36·6	36·4	14,500
„ 14	36·3	36·8	16,200
„ 15	36·4	36·5	14,000
„ 16	36·3	36·8	—
„ 17	36·4	36·7	—
„ 18	36·5	36·5	12,800
„ 19	36·4	36·8	—
„ 20	36·6	—	—

(xiv) *Tetanus.*—As far as I know we have only one record of the relations of the leucocytes in this disease, viz. a case of Schwarz (83), and in this the conditions were altered by the use of Tizzoni's antitoxin. Tetanus in this case was accompanied by a moderate leucocytosis, and the antitoxin appears to have increased it.

(xv) *Cholera Asiatica.*—Virchow and Hayem, and more recently Biernacki ('Deutsch. med. Woch.,' 1895, No. 48), have investigated this disease. These authors agree that there is an excessive leucocytosis (40,000—60,000), especially in the stadium algidum, which quickly declines when the stage of reaction begins. Biernacki states that a pronounced leucocytosis in the stadium algidum is of grave prognostic import, though patients in whom the leucocytosis is slight sometimes die at this stage. Cases in which high values were observed in the reactionary stage ran an unfavourable course.

As C. Schmidt found that the concentration of the blood in cholera was often slight, this large amount of leucocytosis can hardly be entirely due to mere concentration of the blood.

(*b*) *Leucocytosis caused by Malignant Tumours.*—It has long been known that in these cases oligocythæmia and an increase of white cells are sometimes found together. Many (84—90) assumed that this was due to the passage of masses of cancer into the blood, and Andral seems to have been the first to recognise the identity of these cells with leucocytes. Andral and Gavaret's (91) results were confirmed by others (92—94): Lücke (95), who was the first to investigate this question in the living subject, demonstrated an increase of leucocytes in many, if not all cases of cancer. Sappez (96) and Nepveu (97) have confirmed this, and Lücke considered it to be a sign of the generalisation of the disease. Hayem (98) and Alexander (99) were the first to make a thorough study of this subject, which I think is of pathological as well as clinical interest. These authors came to the conclusion that many, but by no means all cases of cancer and sarcoma were accompanied by leucocytosis, sometimes of considerable, sometimes of trifling degree.

It is not necessary that the disease should be of a particular histological variety, nor that it should occur in a particular organ or tissue; there can, however, be no doubt that malignant disease is the cause of the leucocytosis, as this is proved by the disappearance of the leucocytosis after operation. Among more recent observations on this condition those of v. Jaksch, Schneider (100), Pée, and Reinbach (101) should be mentioned.

(1) *Carcinoma.*—Leucocytosis frequently occurs in this disease. There are other causes of the absence or presence of leucocytosis besides the seat of the tumour, its character and enlargement. I give the following examples of individual observations:—Hayem examined fourteen cases of scirrhous mammæ, and found an average of 11,400 leucocytes. Alexander in the same disease found sometimes very high values, *e. g.* 21,700; but sometimes very low ones, 2360 and 3100: in the majority of cases he found about 10,000. In medullary carcinoma of the mammæ he found 10,000—12,000. In scirrhus of pancreas Hayem found 9500, and

Schneider 12,000. In carcinoma of the stomach Hayem found 2608—10,000, and in another series an average of 17,600. This last observation is confirmed by Schneider and Schurg, who found considerable leucocytosis in carcinoma of stomach, Schneider giving values between 16,000 and 20,000. Neither author observed an absence of leucocytosis in carcinoma of the stomach.

With regard to epithelioma, Hayem found an average of 7800 in carcinoma of the uterus, 7200 in epithelioma of the larynx, 6200 in epithelioma of the scrotum, 7100 in epithelioma of the umbilicus, and 7000 in epithelioma of the tongue. In other regions, too, epithelioma showed normal numbers (lip, penis, rectum). Schneider found strikingly high values, too, in a case of carcinoma of the œsophagus and uterus.

The invariable leucocytosis found by Schneider and Schurg in gastric cancer is opposed to Hayem's results. Rieder, also, gives a case without leucocytosis. His results in cancer of other regions sometimes showed considerable, sometimes no leucocytosis; thus he found in four cases of gastric cancer 9400, 14,600, 12,800, and 13,200; in a case of carcinoma of the uterus, 30,800; in cancer of the œsophagus, 6900; of the vagina, 9800; and of the lip, 11,600.

It is difficult to deduce a regular rule from these observations. The conflicting results make it improbable that the leucocytosis is determined by the seat of the disease. The histological nature, too, of the tumour seems to be of subordinate value; *e. g.* Hayem found 2360 in mammary scirrhus, and in another case 21,700. A certain influence, to which I draw attention, seems to me able to account, in part at least, for these differences. Grawitz (102) had shown that injections of extract of cancer nodules into rabbits caused a flow of lymph from the tissues into the blood-vessels, so that dilution occurred. Now we know from other pathological conditions (post-hæmorrhagic leucocytosis) that under such circumstances an increase of leucocytes ensues in the blood, which is due, in part at any rate, to these cells flowing in with the lymph. We may assume, then, that leucocytosis occurs in cancer when absorption of cancer takes place.

Cases are sometimes seen which seem to confirm this view, when a secondary softening of the tumour is followed by an increase of leucocytes.

			Leucocytes.
K. K—, æt. 59.	Abdominal carcinoma,	Jan. 19	18,541
	,, ,,	,, 21	52,166
	,, ,,	,, 24	64,750
	,, ,,	,, 26	68,000
	,, ,,	,, 28	80,514

Post-mortem.—Softened carcinoma of left kidney with secondary nodules in supra-renal and retro-peritoneal glands.

Hayem's observations of the effect of operation on the number of leucocytes are of interest.

	Number of leucocytes.	
Carcinoma.	Before operation.	After recovery.
1. Scirrhus of breast	21,700	6200
2. ,, ,,	11,500	6200
3. ,, ,,	11,000	8400
4. ,, ,,	10,000	9000

If the cancer causes the leucocytosis, then removal of the tumour is usually followed by a loss of leucocytes.

(2) *Sarcoma.*—In this disease our results are much more uniform than they are in cancer. In the great majority of cases a leucocytosis exists, which sometimes is so intense that it is mistaken for leukæmia (Palma, 103). Hayem found in a case of osteosarcoma 11,250 before and 5270 after operation. It is not yet decided whether the white cells in the blood in these cases are neoplasms or true leucocytes. I found that the increase was due not only to polynuclear but also to mononuclear cells. Rieder does not confirm this.

No.	Observer.	Diagnosis.	No. of leucocytes.
1	Hayem	Osteosarcoma	11,250
2	Alexander	,,	52,700
3	,,	,,	15,900
	,,	,,	15,570
4	,,	,,	13,020
5	,,	,,	10,950
	,,	,,	12,090
6	,,	,,	16,430
7	,,	,,	16,275
	,,	,,	17,050
8	,,	,,	11,248
9	Rieder	,,	12,700
	,,	,,	10,900
	,,	,,	6,000
10	,,	,,	9,100
11	,,	,,	8,000
12	Limbeck	,,	32,000
	,,	,,	26,800
	Hayem	Lymphosarcoma	11,700
	Alexander	,,	11,696
	,,	,,	19,910
	,,	,,	19,530
	,,	,,	10,540
	,,	,,	11,470
	Limbeck	,,	38,000
	,,	,,	10,800
	,,	,,	55,100
	Rieder	Melanosarcoma	28,500
	,,	,,	22,300
	,,	,,	41,600

(*c*) *Post-hæmorrhagic leucocytosis.*—It is well known that an increase of leucocytes is seen in the blood immediately after a severe loss of blood. Our knowledge of the course and causes of this leucocytosis is more complete than it is in many other cases on account of the number of observations upon it (104—106).

A dog, weight 1510 g. At 6 a.m. 32 c.c. of blood withdrawn.

	Number of red corpuscles.	Number of leucocytes.
Before	4,480,000	9,900
Directly after	4,900,000	9,660
6.35	4,410,000	15,416
6.50	3,200,000	16,560

This leucocytosis does not disappear rapidly, but may last for some days.

Dog, weight 8150 g. March 27th, 3 p.m. 420 c.c. of blood withdrawn and replaced by equal amount of normal saline solution (Rieder, loc. cit.).

			Number of leucocytes.
March	27th	8 a.m.	8,600
,,		4 p.m.	13,300
,,	28th	8 a.m.	10,200
,,	30th	3 p.m.	14,600
,,	31st	,,	17,000
April	4th	9 a.m.	18,200
May	1st	,,	7,100

In another experiment the leucocytosis lasted twelve days.

This continued leucocytosis cannot be due simply to the loss of blood, for a traumatic injury in itself without loss of blood can cause a certain amount of leucocytosis. In hæmorrhage, again, from other causes, *e. g.* ulcer of stomach, the resulting leucocytosis disappears much more quickly.

J. A—. Gastric ulcer. October 21st. Severe hæmatemesis.

October 22nd. Number of leucocytes 18,500.
,, 25th ,, ,, 9,200.

H. A—. Gastric ulcer. July 9th. Severe hæmatemesis.

July 10th. Number of leucocytes = 19,100.
,, 12th. ,, ,, = 8,300.

There is no doubt that the origin of post-hæmorrhagic leucocytosis lies in the resulting dilution of the blood, which is caused by a flow of lymph with leucocytes. The old view—that the relatively great viscidity of the leucocytes caused a comparative retention of these cells—is negatived at once by the fact that the leucocytosis does not reach its height for some time. If this view were correct the number of leucocytes would be at a maximum immediately after the hæmorrhage.

(*d*) *The leucocytosis of the death agony.*—Litten (107) in

1883 drew attention to the observation that leucocytosis almost always appeared in the death agony even of individuals who showed no leucocytosis during their disease. This leucocytosis was thought by him to be constant, developing in a few days, gradually increasing, and being proportional to the length of the agony, but independent of the cause of death. Litten's results are not convincing, as his accounts are not full, thus complete descriptions of the cases and of the absolute numbers of leucocytes are absent; again, he had but little knowledge of inflammatory leucocytosis. Of late years the point has received little attention—in fact, only Rieder discusses it; he gives four cases, three of which showed leucocytosis during the agony. Unfortunately it is not clear, even in these cases, whether there was not an obvious cause for the leucocytosis, *e. g.* hypostatic pneumonia, which is so common an antecedent of death. My opinion is that we are not justified in speaking of an agony leucocytosis. The moribund show very different relations. If leucocytosis exists during the disease (*e. g.* in pneumonia) it often diminishes, but sometimes increases at the last; whereas if leucocytosis is absent it may remain absent until the end. There is, however, often a rapid increase of leucocytes in the last days or hours of life, and in these cases I have always been able to find a cause for the leucocytosis, *e. g.* patches of pneumonia or bronchopneumonia, septic bronchitis, or hypostatic pneumonia. As a rule, according to my observations, the cause is an inflammation of the respiratory passages, so that the existence of an increase of leucocytes due to the death agony is more than questionable.

C. Leucocytosis due to Therapeutic and other Influences.

The first observations on the influence of drugs on the number of leucocytes are those of Hirt (108). He found that the number of leucocytes increased under the influence of certain tonics, *e. g.* tinct. myrrh, quinine, etc. H. Meyer (109) (a pupil of Binz) examined the effect of a number of ethereal oils, *e. g.* oil of turpentine, of cinnamon, and of peppermint, and confirmed this observation. Lately Pohl (110) has demonstrated the leucocytotic effect of a large number of drugs—tonics, stomachics, and rubefacients,—and has shown the analogy of this action with that of albumens in the intestine. Amongst the substances examined by Pohl, the aromatic bodies in fruits and spices (*e. g.* oils of fennel, peppermint, and aniseed) and bitters (absinthe, extract of gentian) were especially active; whilst inorganic combinations (*e. g.* hydrochloric acid, sodium bicarbonate) did not act or acted irregularly (*e. g.* oxide of iron, nitrate of bismuth). The same is true of some of the volatile fats and of alkaloids—some, *e. g.* acetic ether and piperin, exciting leucocytosis; whilst others, *e. g.* ethyl-alcohol, caffeine, and quinine, have no effect.

Example of Pohl's starving dog:

	Number of leucocytes.
9.55 a.m.	12,950
10.5	2 c.c. of Ol. Fœniculi in 2 c.c. of water.
10.35	22,392
11.5	28,172
11.45	salivation and vomiting
12.5	22,682
5.5	18,630

We see that leucocytosis rapidly follows, and lasts for some hours. An inorganic solution showed less chemiotactic action:

Dog, weight 4790 g.

	Number of leucocytes.
4.0 p.m.	15,013
4.40	14,521
4.45	0·25 g. Ferr. Oxid. Dialys.
5.45	23,704
6.45	20,864

Pohl gave substances by the mouth, but in later experiments subcutaneous or intra-venous injections have been largely used. In this way Löwit (111) found that hemialbumose, peptone, pepsin, nucleic acid, nuclein, leech extract, pyocyanin, tuberculin, curare, and urea first caused a diminution, but eventually an increase of leucocytes. Goldscheider and Jacob (112) made extracts of different organs, and found differences in their action. Extracts of spleen, thymus, and bone-marrow on subcutaneous injection caused primary diminution and secondary increase of leucocytes. Extracts of thyroid, liver, kidneys, and pancreas had no effect. Recently Winternitz (113) has made a comprehensive study of this matter with the object of determining whether a connection existed between the local action on the tissues and the change in the composition of the blood. A local inflammatory œdematous swelling appeared after subcutaneous injections of neutral salts, and generally lasted for some twenty-four hours; the leucocytosis was small, the increase being about 40—75 per cent. of the original number. There was also only a moderate leucocytosis, in proportion to the surrounding inflammation, if necrosis was caused by injection of acid or silver nitrate solutions. Considerable leucocytosis usually followed, with local necrosis and aseptic suppuration, if, on the other hand, cutaneous irritants (*e. g.* oil of mustard, thiosinamin, oil of turpentine, croton oil, etc.) were used. Subcutaneous injection produced but moderate effects, when contrasted with Pohl's observation of the powerful leucocytotic effect produced by the administration by the mouth of proteids (egg-albumen, sodium albuminate, and peptone). The usual increase was about 6 per cent. Winternitz divides the substances he examined into two groups according to their local action on the tissues, viz. according as they produce necrosis, round-cell infiltration, and œdema. He finds the amount of leucocytosis proportional to the intensity of the local reaction. The first group (salts and simple corrosives, such as free acids and alkalies) give rise to small local reaction and trivial leucocytosis. The second group, "true stimulants" (turpentine, mustard, croton, etc.), cause suppuration and a large amount of leucocytosis.

Here we see again the connection between exudation and leucocytosis. It is impossible to give an account of all the substances that have been examined with regard to their leucocytotic effect. As has been said above, the majority of observers consider that the proteins of micro-organisms or their products are the cause of this leucocytosis, but they are always obliged to fall back on the mystical chemiotaxis; so in summing up this question of therapeutic leucocytosis we can only say that, in addition to products of micro-organisms, there are many chemical bodies and mixtures that cause an increase of leucocytes in the circulation, usually after a preliminary diminution. The appearance of the increase, its duration and magnitude, depend, as we have seen in inflammatory leucocytosis, on the amount of the dose and the individuality of the organism.

In addition to medicinal bodies, *i. e.* influences which probably act chemically, there are a number of influences which act on the leucocytes in a different manner, *e. g.* Löwit found that chaining up rabbits invariably caused a diminution of leucocytes in the peripheral vessels. The gradual cooling that animals undergo when fastened up produces the same effect. So does shock produced, for example, by a blow on the neck of a rabbit.

The effect of *hot and cold baths* probably depends on vaso-motor action. Winternitz (114), Rovighi (115), Knöpfelmacher (116), and Thayer (117) have examined this effect, and agree that cold baths increase the number of leucocytes in the peripheral vessels, whereas hot baths decrease it.

The following is an example from Knöpfelmacher:

		Number of leucocytes.
(i)	Before bath at 19° C.	9,630
	10 minutes after	14,670
(ii)	Before	11,770
	10 minutes after bath at 18° C.	14,760
	30 ,, ,, ,,	13,590
(iii)	Before	8,130
	8 minutes after bath at 40° C.	4,070
(iv)	Before	9,810
	15 minutes after bath at 42° C.	8,840

Rovighi observed the same results in diseases such as typhoid. There is now hardly any doubt (118) that these phenomena are due simply to concentration or dilution of the blood brought about by the contraction or dilatation of the vessels.

THE PLATELETS.

These were described in the year 1882 by Bizzozero (119) as the third elementary constituent of the blood, but had been previously noticed by others (120—124). The hæmatoblasts described by Hayem (125) in 1877 are identical with them The platelets (or disclets [Laker, 126]) are small circular or ovoid bodies which are devoid of hæmoglobin, sometimes finely granulated, and characterised by an extraordinary fragility. Their diameter is much less than that of a red corpuscle, and according to Bizzozero (127) is from 3 to 3·5 μ. They stain lightly with aniline dyes, and are amphophile. They are characterised, in addition to their fragility, by great adhesiveness, so that they readily cling to the corpuscles or to one another, and in preparations are usually found in clusters. The specific weight seems to be very high (128). Löwit (129) held that they are not original constituents but artificial products, formed partly by precipitated globulin and partly by destruction of leucocytes. Laker (130) and Bizzozero demonstrated their existence, however, during life in the vessels of the broad ligament, so that the majority of histologists adhere to the belief in their pre-existence in the blood (131). Their high specific weight and adhesiveness seems to give them an important place in the stanching of blood by forming the so-called white thrombus (132). It is not known whether they have any.other function. We come across them clinically in almost every preparation, and so find great differences in their numbers in different cases. Their physiological number was estimated by Afanassiew (133) at 200,000—300,000, by Fusari (134) at 180,000—250,000, and by Pruss (135) at 500,000 per c.m. The estimation is difficult, as the preparation must be made very rapidly to avoid the slightest degree of clotting, for then the platelets adhere to one another. The effect of physiological influences on their number has not yet been observed. An increase of platelets occurs in anæmia, especially when the condition of the blood is improving. Fusari stated that the diameter increased in anæmia as soon as convalescence was established. There is an increase also after loss of blood, and in leukæmia. After certain poisons (pyrogallic acid, glycerine, Lugol's solution) a diminution is said to exist, which is followed on recovery by an increase. The number is said to diminish in high fever, except in the case of tubercle and pneumonia. Pizzini (136) finds that in fevers the platelets diminish proportionately to the increase of temperature, and the more rapid the course of the fever, the greater the diminution of platelets. In malaria they sometimes disappear completely. After the temperature falls there is an increase of platelets which reaches a maximum in six to seven hours after the crisis. In anæmia an increase of platelets is a good prognostic sign. In certain physiological conditions (baths) the behaviour of the platelets is analogous to that of the leucocytes.

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III. The Blood Parasites.

A. The Parasites of Malaria.

Almost all micro-organisms of pathological moment may be, at some time or other, found in the blood, but it is well to restrict the term blood parasites to those organisms which run their course of development in the blood, and exert a destructive influence upon it.

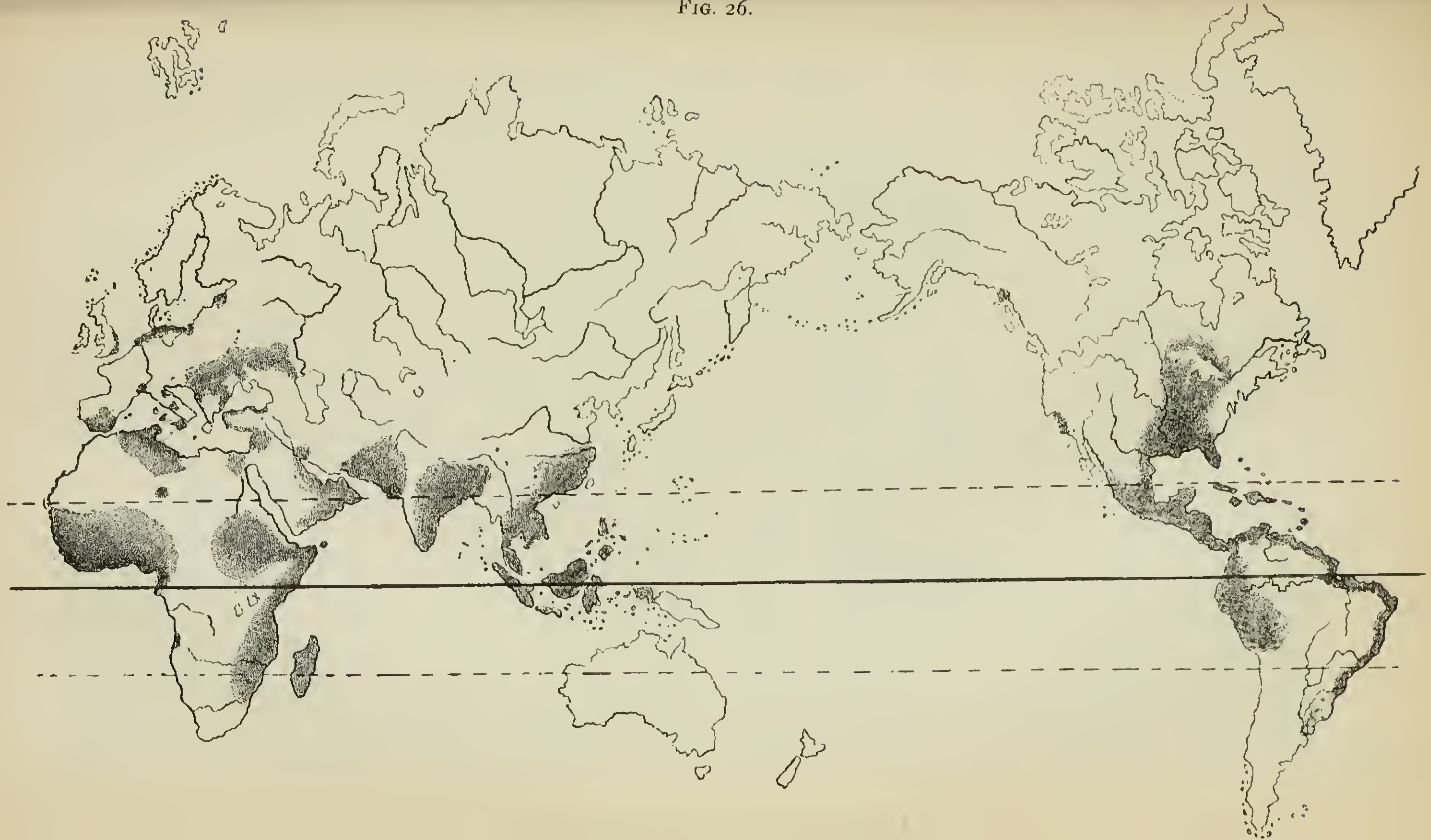
The parasites of malaria are the most important members of this group. We exclude the more highly organised parasites, *Filaria sanguinis hominis* and *Distomum hæmatobium.*

Long before these organisms were known several apparently analogous pathological conditions were classed together under the heading of malaria. This classification was justified by Laveran's important discoveries, which showed that these conditions were due to certain similar though not identical causes. Previous to this time investigations had, in the main, been directed towards the conditions under which these fevers originated, as this was a matter of more practical interest.

In the following map (Fig. 26) the districts in which malaria is most rife are marked. It is well known that the disease is most widely spread in countries bordering on the equator. This region extends from 50° N. to 40° S. Certain districts, such as the courses of large rivers, *e. g.* the Mississippi, Ganges, and Volga, are characterised by the existence of a large amount of malaria, as also are some plains, both low-lying and high, such as South Russia and Hungary on the one hand, and Hindostan, Mexico, Peru, and Colombia on the other. Many causes affect the ætiology of this disease besides these geographical relations, *e. g.* time of day, season of year, atmospheric currents, and humidity. Excessive rain and extreme dryness are unfavourable to it; it is, in fact, most prevalent under conditions of uniform humidity.

In cases, such as the building of the Suez and Panama canals, where great disturbances of earth take place, the incidence of malaria is largely increased. Bad hygienic

FIG. 26.



conditions exert a marked influence, but age and sex are of subordinate importance.

Theories as to the mode of infection were purely speculative until quite recent times.

Hirsch introduced two boxes of malarial earth into a house in a district absolutely free from the disease, as some circumstances seemed to indicate that the abode of the poison, outside the body, was in the earth. The tenants acquired malaria.

Other facts seemed to indicate the existence of the poison in air or in water.

It was in 1880 that Laveran, by his discovery of the "Plasmodium malariæ," laid the foundations of our knowledge on this subject.

Mitchell (3) and Klebs and Tommasi Crudeli (4) had previously described organisms obtained from the mud and air of marshes, but these were proved not to be the exciting causes of malaria.

The disease can be inoculated from man to man, although it is not contagious. Schellong (1) states that his nurses frequently contracted malaria.

All attempts to cultivate the parasite have so far failed, both in the ordinary culture media and inside the bodies of the lower animals. The parasites remain alive in the leech for about forty-eight hours (Rosenbach, 2). The most important observations, in addition to Laveran's work (5), are those of Marchiafava and Celli (6), Golgi (7), Mannaberg (8), and lastly, of Manson and Major Ross.

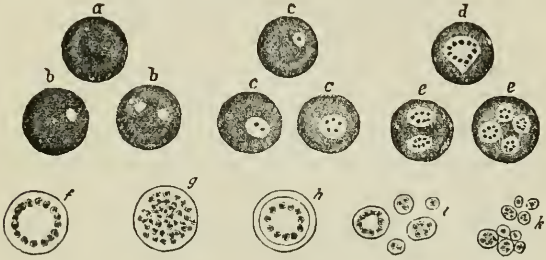
The parasite which was discovered by Laveran, and which is now universally acknowledged to be the exciting cause of malaria, is known as the "Plasmodium malariæ." This name, suggested by Marchiafava and Celli, is a most unsuitable one; for a plasmodium is formed by the union of a number of amœbæ which retain their nuclei, whereas the malarial parasite is almost invariably mononuclear. It is now generally considered (Metschnikoff, 9) to belong, zoologically, to the sporozoa in the genus Coccidium (Pfeiffer and Simond, 'Annales de l'Institut Pasteur,' July 27th, 1897).

On microscopic examination of the blood, the parasites may be seen in a variety of forms, which may be roughly divided into spherical, flagellated, and crescentic bodies.

We must, however, remember that there is not one single specific parasite of malaria, but that there are a number of different ones. It is nevertheless true that these are closely allied to one another.

(1) *The spherical bodies* (Fig. 27).—These, the commonest forms, are small, flattened, hyaline discs of protoplasm, varying in size from 1 μ to that of a red corpuscle. Scattered through this pale body are a number of particles of intensely black or reddish-black pigment—*malarial pigment.* This pigment is formed from the hæmoglobin by the parasites. It is insoluble in concentrated mineral acids, is stained yellow by concentrated alkalies, and is soluble in ammonium sulphide. The granules vary greatly in size, and are coarsest in the quartan form. The bodies also contain vacuoles. The amœboid movements of the plasmodia are of special importance, and are most obvious in the young forms. Those of the tertian parasite are more intense than those of the quartan, and those in the pigmentless form of "pernicious fever" than those of the tertian. In addition to this we can see, in unstained preparations, a more or less marked motion of the pigment in the form of currents, the activity of which is dependent on the form of parasite, and is most marked in the tertian variety.

FIG. 27 (after Laveran).



The spherical bodies appear free in the plasma (ectoglobular), as well as inside the red corpuscles (endoglobular), and it is stated that they may also be superimposed on the latter. The infected corpuscle gradually loses its colour with the growth of the parasite, and pigment is formed. Sometimes, in the simple tertian form, we get an increase in the volume of the blood-cell, whilst in other forms, where no pigment is formed, the corpuscles become diminished in size, acquiring a colour like that of old brass. The propagation of the mature parasite takes place, at the cost of its existence, by sporulation.

The pigment becomes arranged centrally in a spoke-like formation, and small bright bodies with a nucleolus are formed by the parasites, so that grape-like figures are produced. In the quartan type these were described as *marigold* forms. In these the pigment is contained centrally, and around it are usually about ten spores, arranged like the petals of a blossom. The spores gradually swell up, and are dispersed when the corpuscle breaks up. The latter, with the pigment granules, are taken up by phagocytic leucocytes and deposited in the spleen. In the tertian form a larger number of spores is usually formed (fifteen to twenty). These are smaller, have also a nucleolus, and are grouped round the central pigment in the form of a sunflower (Golgi).

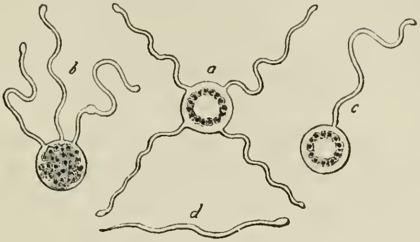
These marigold and sunflower figures are more rarely seen than the accounts of these authors would lead us to think. Both groupings often occur irregularly, so that sometimes a few spores are seen arranged round the pigment in no particular form. The number of spores, however, is always an important sign in the differential diagnosis of the tertian and quartan parasites.

The free spore attaches itself to a red corpuscle, and continues to grow, with formation of pigment, until it becomes mature. The granules of melanin are in the first instance deposited in the periphery, and it is only shortly before the beginning of sporulation that they become arranged in the centre.

Thus a study of these spherical bodies shows us what is called the "*intra-corporeal or human cycle*" of the parasites; also an "*extra-corporeal cycle*," in which the next form plays an important part.

(2) *The flagellated bodies* (Fig. 28).—These are not uncommonly seen in specimens of fresh malarial blood examined some time (ten to thirty minutes) after mounting.

FIG. 28 (after Laveran).



They are composed of colourless protoplasm, with dark melanin granules and a number of very delicate and pliant filaments; but they differ from the spherical bodies in that they are always ectoglobular. The filaments are about three to four times as long as a blood-corpuscle is broad, exhibit very violent oscillatory movements, and may possibly be hollow, seeing that small swellings containing granules of pigment are sometimes found in their continuity.

Occasionally one of the filaments breaks off and swims about free. Laveran thought these bodies were mature forms of the parasite, as he noticed that they were usually formed just before the onset of fever. Danilewski (12) agreed with him, but Grassi and Faletti (13), and Marchiafava and Celli (14) took them to be moribund forms.

Crescent bodies also show flagella.

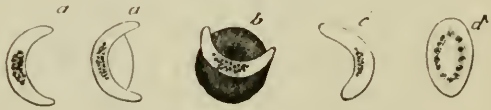
The fact that the flagellated body does not come into existence until the blood has left the vessels suggested to Manson that their function lay outside the human body. This was the foundation of the theory of the extra-corporeal life of the parasite enunciated by Manson and proved by Major Ross. The flagella are fertilising elements, and perform their sexual function in the bodies of mosquitoes (Anopheles). The resulting fertilised body is known as a zygote. Development within the zygote takes place by the formation of a number of *blasts*—a number so large that the zygote capsule is tense and ultimately bursts, shedding the blasts into the body-cavity of the mosquito. They are then conducted to and stored up in the veneno-salivary gland, from which the vertebrate host is again infected.

After infection the youngest parasites are known as *amœbulæ.* They develop into sporocytes and gametocytes. The *sporocytes* divide into spores, which escape into the blood, invade fresh corpuscles, and repeat the cycle. In this way the parasite is propagated indefinitely in the vertebrate host.

The *gametocytes* may resemble the sporocytes, but in some varieties take the form of crescent bodies. They are transferred to the stomach of the anopheles, escape from the blood-cells, and are seen in two forms as hyaline and granular cells. These may be considered as male and female, the former producing flagella, which impregnate the latter. Thus the extra-corporeal cycle of the parasite is completed.

(3) *The crescent bodies.*—These are transparent cylindrical figures, semilunar in shape, which remain unstained, and usually contain some dark granules of pigment and sometimes small vacuoles in the centre of their convex boundary. Their maximum length lies between 8 and 9 μ, and their breadth is about 2 μ (Fig. 29).

FIG. 29 (after Laveran).



They are found free in the plasma and inside the red corpuscles. They possess a cuticle, exhibit no amœboid movements, and their pigment is at rest.

There are, however, variations of this type; thus the crescent has repeatedly been observed to develop into a spindle-shaped and then into a spherical body. When this happens the pigment has at first a coronoid arrangement; it then acquires movements of a jumping character and loses its regular arrangement, whilst the filament formation described above takes place. With a suitable lens a fine line can often be seen between the angles of one of these crescent bodies; this represents the remnant of the stroma of a red corpuscle.

These bodies have also been seen to undergo another change by segmentation (Grassi and Feletti, 15), which takes place transversely, usually in the centre of the body.

The biological significance of these forms is a matter of great interest. Laveran originally took them to be cysts with the power of developing flagella. Councilmann (16) thought them spores, others (17) sterile products of the amœboid forms; whilst Mannaberg sees in them a process of copulation between two or four parasites, and maintains that he has seen, under the microscope, two spherical bodies join together and form a crescent.

These crescent bodies seem to occur only in those cases that lead to severe cachexia and anæmia, especially in the tropics and certain districts in central Europe. Such cases may run their course with atypical fever, continuous fever, or no fever at all. The bodies are said never to occur in the mild cases of tertian and quartan fever that are the rule in Europe. I, however, found them in the blood of a man suffering from tertian fever who had lived all his life in Vienna.

The following are the varieties of malarial parasites that can be distinguished:

(*a*) The parasite of typical quartan (Golgi).
(*b*) ,, ,, typical tertian ,,
(*c*) ,, ,, pernicious quotidian (Marchiafava and Celli).
(*d*) ,, ,, malignant tertian (Marchiafava and Bignami).

We may also have infection by a mixture of these parasites.

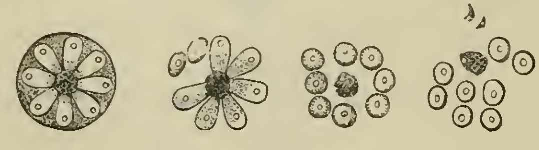
Laveran's original idea was that the different forms were due to variations of a single parasite. But this view is now abandoned, for the results of inoculation show that one particular form of disease is uniformly propagated by one form of parasite. The typical tertian and quartan fevers follow a definite course, and are each caused by a definite parasite. The quotidian form, however, differs in that it may be caused not only by its own parasite, but also by inoculation with two generations of tertian parasites or three of quartan, which reach maturity at intervals of twenty-four hours. If the difference is not exactly twenty-four hours the attacks of fever occur irregularly.

The true quotidian parasite of Marchiafava and Celli develops in twenty-four hours.

The parasite more recently described by Marchiafava and Bignami causes a true tertian fever, which runs a course of a very pernicious character, and is distinguished from Golgi's tertian parasite by the formation of crescent-shaped bodies.

(*a*) *The parasite of typical quartan fever.*—The chief characteristic of this parasite is that its period of development is seventy-two hours. In its initial stage it appears in the infected corpuscle as a light unpigmented spot, which, in fresh preparations on a warm stand, shows amœboid movements. After about twenty-four hours it is increased in size, and has coarse granules of pigment in its periphery, whilst its power of motion is almost lost. The parasite gradually increases in size until it occupies the whole cell, which disappears. Whilst this is going on the granules take on a sort of hopping motion, and arrange themselves centrally in a spoke-like formation; at the same time segmentation occurs (there are usually from six to eight segments), whilst the so-called marigold forms may be produced (Fig. 30).

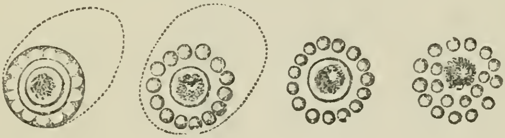
FIG. 30 (after Laveran).



In each segment we can observe a light spot; this is the nucleolus of the future spore. The sheath investing the spores bursts shortly before or during the attack of fever. The red corpuscles do not swell under the influence of the quartan parasite.

(*b*) *The parasite of typical tertian fever.*—The period of development of this parasite is only forty-eight hours. It goes through the same stages as the quartan, but more rapidly. The amœboid movements are of a livelier character, and the granules are finer. The red corpuscle loses its colour much more rapidly, and sometimes increases considerably in size. In this case also the formation of spores indicates the onset of fever, but the number of spores formed is about twice as great. They are much smaller, are circular in shape, and are generally arranged in the form of a sunflower or bunch of grapes (Fig. 31). Sometimes the pigment is concentrated at the periphery (Golgi); this is taken to be a sign of degeneration (Antolisei). Flagella can be seen to be protruded from the adult forms a few minutes after a fresh preparation has been made. The following comparative table (p. 258) of the characteristics of the tertian and quartan parasites is given by Mannaberg. In both forms at the onset of fever we may find spherical bodies which are not sporulating, but are approaching maturity. This is because infection has taken place with different generations of the parasite, which do not become mature simultaneously. In addition we must remember that all mature parasites do not undergo sporulation, and take care consequently in drawing conclusions from the table. In order to foretell the time of the next attack we must observe the stage of development of the oldest forms.

FIG. 31.



There is no difficulty in recognising a duplex tertian or triplex quartan case when we find immature forms in conjunction with others that have already reached the stage of sporulation.

(c) *The parasite of true quotidian.*—The small size of these is striking, and they differ from the above forms in that they show the crescent-shaped bodies. The latter, according to Mannaberg, multiply by transverse segmentation, but Canalis states that the process is one of sporulation. The quotidian parasite develops in twenty-four hours.

Comparative Table of the Characteristics of the Quartan and Tertian Parasites.

	Quartan.	*Tertian.*
Within 12 hours after onset.	Small, indolent, or motionless unpigmented parasites lying on the red corpuscles.	Smaller, active, attached to or even already inside the red corpuscles.
Within 24 hours.	Some have a few granules at periphery, others still unpigmented; size about one sixth to one fifth of a red corpuscle.	Larger, about one third of red corpuscles. Very fine granules, movements still active, the infected red corpuscles pale and enlarged.
Within 36 hours.	—	Occupy two thirds to four fifths of red corpuscles, which are pale and enlarged, irregular shape, changing slowly; granules numerous, now coarser, and moving so actively as to shake the whole parasite.
Within 48 hours.	Occupy one half to two thirds of the red corpuscles, strongly pigmented, mostly circular, no amœboid movements, pigment quiescent.	Large, round, filling almost the whole red corpuscle; pigment in some parts active, in others at rest; sporulation.
Within 60 hours.	The red corpuscle so completely occupied that only a narrow border is left.	—
Within 66 hours.	In many parasites no portion of the affected red corpuscles can be seen; pigment in spoke-like formation; in places signs of commencing sporulation.	—
Within 69 hours.	In some bodies sporulation complete, in others in progress, with pigment concentrated at centre.	—

At first it is unpigmented, and is characterised by very active movements. It could hardly be distinguished from the red corpuscle if it were not for these movements. After a short time the power of motion ceases, and there is formed in the corpuscle either a central light space with a red spot in the middle, or a figure described as "cricoid" (signet-ring shaped), which is produced by a button-like projection from the periphery. From the latter the parasite can return to the amœboid form. It is customary to divide these parasites into two classes according as they produce pigment or not.

The so-called pigmented parasite of summer fever, described by Marchiafava and Celli, produces a pigment which is often merely reddish in colour and exceptionally finely granulated. The activity of its movements is moderate. According to these authors sporulation is seldom seen in blood taken from the peripheral circulation. It, however, occurs as usual, at the onset of the fever, in the internal organs. The red corpuscles are not swollen ; on the contrary, they shrink in size, and their colour becomes like that of old brass (brass corpuscles). Crescent-shaped bodies appear, and often remain long after the fever has subsided. The appearance of new primary amœboid forms indicates the approach of another attack of fever.

The unpigmented form differs only in the absence of pigment. Brass corpuscles are formed, sporulation takes place in the internal organs, and the crescent bodies appear. The latter, however, are pigmented ; it is only when the patient does not survive the formation of crescent bodies that there is no formation of pigment. Clinically, infection with the true quotidian parasite is followed by obstinate and pernicious fever ; this may cease for weeks and then reappear. The form of the fever may be truly quotidian, or when several generations of the parasite are present, continuous or irregular. The anæmia that follows is particularly severe. In stained preparations the differences between the amœboid form of this parasite and those of tertian and quartan are not marked. Hence it is essential to examine a drop of fresh blood for the purpose of making a differential diagnosis.

(*d*) *The parasite of malignant tertian fever* is akin to that of quotidian, but its development takes forty-eight hours. Pigment is not formed until the lapse of twenty-four hours. Sporulation, in this form also, takes place in the internal organs. The red corpuscles shrink and crescent bodies appear. This parasite causes a severe fever of tertian character. The fever may be continuous or irregular if several generations are present, or a form may ensue in which we get high fever for two or three days with periodic remissions. There are intermittent fevers in which many different parasites are found in varying stages of development in addition to the definite forms I have described. These are called "mixed infections," and in them the course of the fever is the resultant of the actions of the different parasites.

Quinine has a marked effect on the malarial parasites. Their mobility becomes impaired, and products of degeneration are formed in them, which are called "quinine forms," and are to be taken as signs of necrosis of the parasites. The spores in the forms undergoing segmentation (marigold, etc.) are particularly sensitive to the action of this drug. One result is that they no longer show a nucleolus, and Mannaberg calls them "still-born." The adult forms are not so sensitive, and the crescent bodies are wholly unaffected.

As the malarial parasites destroy the red corpuscles, there must be a deficiency of these cells, and anæmia was known to be a complication of this disease long before the discovery of the exciting cause. It is only recently that systematic investigations have been made into the constitution of the blood, and further researches are still desirable, especially for tropical cases. Hayem (19), Halla (20), and Limbeck found the number of red corpuscles in tertian cases diminished to 2·5, 2·8, and 1·182 millions respectively. Kelsch (21) and Dionisi (22) found as few as ·5 million in pernicious cases. Kelsch estimated that during an attack the number lost was approximately one fifth of the total number, and Dionisi that the number lost varied between 200,000 and 1,000,000.

The majority of observers find that the decrease of hæmoglobin and the diminution of red corpuscles are proportional, but Kelsch and Kiener (23) have described a condition of relative oligochromæmia during the period of convalescence. This has been, partly at any rate, confirmed by Mannaberg, and is to be taken as a sign of regeneration.

As regards the leucocytes, there is never an increase but often a diminution in the apyrexial periods and at the onset of fever. Billings (24), however, has shown that in the post-febrile periods there is sometimes a high degree of leucocytosis, *e. g.* 30,000 or 40,000. The explanation of this is to be found in the associated anæmia.

The leucocytes, especially after the attack of fever, contain melanin granules; this, according to Metschnikoff, is a phagocytotic phenomenon. Whether this tends to spontaneous cure or not is a contested point, but other facts, *e. g.* that the fever itself has a damaging effect on the parasites, and that numbers of them remain sterile after the attack, seem to be of more importance than phagocytosis.

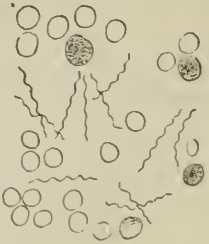
It has of late been considered that this detrimental action of the parasites is increased by the production of some poison. Fever has been observed in malarial individuals in the absence of sporulation, and even when no parasites were observable in the blood (Baccelli [25]). The observations of the decrease of the toxicity of the urine during the attack (Roque and Lemoine [26]), and of the increase of the toxic action of the perspiration of malarial individuals (Queiroli [27]), also point to this view.

The significance of the demonstration of malarial parasites in the blood is as great as that of tubercular bacilli in the sputum. Negative results do not exclude the disease, but one positive result is conclusive. In other respects, too, examination of the blood is of practical utility; *e. g.* if crescent bodies or brass corpuscles are found the prognosis is relatively bad, and the probability is that quinine will be ineffective.

B. The Parasite of Recurrent Fever.

This, the spirochete of Obermeier (28), is of especial interest, being the first parasite to be recognised as the exciting cause of an infectious fever. The spirilla are delicate, motile, structureless filaments with a corkscrew-like appearance. Their length is about six times that of the diameter of a red corpuscle (Fig. 32). The curvature can be seen to vary; its diminution may cause a two- or three-fold increase of the length of the parasite. The movements are of an undulating character and are very graceful. Movements of flexion and extension may also occur which possibly are due to the presence of cilia. The whole or only a portion of the parasite may participate in both these forms of motion; in the latter case part of the parasite may remain absolutely motionless. In addition to these movements, which are usually fairly rapid, the spirilla have a forward motion of a much more indolent character. Sometimes two or more may be, as it were, screwed into one another, thus giving the appearance of a parasite of exceptional length. If a number of them are intermingled we get a "nest," a figure of a finely granulated appearance which may simulate a leucocyte. Filaments (motile) may project from this, or it may enclose blood-cells.

FIG. 32 (after v. Jaksch).



In spite of the amount of work expended on the study of this parasite, our knowledge of its biology is meagre. We practically know nothing more than that the spirillum is always present in the blood at the onset of an attack of recurrent fever, and that it is found in no other disease. Its diagnostic significance is therefore comparable with that of the plasmodium in malaria. As a rule it is not to be seen in the apyrexial periods, but in exceptional cases it may be observed just before or just after the onset of the fever. Thus Heydenreich (29) found it twenty-four hours before the onset, and Birch-Hirschfeld (30) for two days after the decline of the fever. The number of spirilla present at the beginning of the illness is usually very small. Moczutkowsky (31) found at this period only one spirillum in from twenty to thirty fields of view. The number increases in the subsequent attacks, so that on corresponding days of two attacks the spirilla are more numerous in the later one. The number of spirilla is not, however, proportional to the severity of the disease nor to the height of the temperature. In two cases of equal severity the numbers may be totally dissimilar. This is attributed to the fact that the parasites are very short-lived and are rapidly regenerated, so that it would be merely a coincidence if equal numbers were found in the blood of two patients, even at the same stage of the fever. It must also be remembered that the spirilla are not uniformly distributed in the blood, but that the number varies considerably in specimens of blood taken from different parts of the body. Albrecht (32), by direct observations, demonstrated that the spirilla were rapidly generated. In one preparation in which there were at first only a few scattered here and there, the increase was so great that after six hours there were several in each field of view. After the decline of the fever the spirilla become sluggish and then break up into small granules, the ultimate destination of which is unknown. It seems probable that spores are formed, but of this matter nothing is definitely known. Sarnow (33) and von Jaksch (34) have noted the appearance of small glistening bodies resembling diplococci during the apyrexial period. These were especially numerous just before the attack, and, according to von Jaksch, grew into short thick rods from which spirilla developed.

Attempts to form cultures have with one exception, viz. that of R. Koch, failed. There is no direct record of Koch's results, but Rossbach (35) mentions some letters and photographs that Koch sent to F. Cohn, in which the former states that he cultivated the spirilla in the same way as anthrax bacilli, and that they grew into long spiral filaments intermingling with one another and forming long plaits which retained the characteristic undulations.

The results of inoculation have been more successful. Carter (36) and Koch (37) injected defibrinated blood taken from patients suffering from recurrent fever into small apes. These contracted the same disease (with some modifications), and the spirilla multiplied in their blood. Heydenreich succeeded in keeping the parasite alive for one hundred and eighty days in sealed glass tubes, and studied the conditions of their vitality. Although they seem to need oxygen (in defibrinated blood in which the corpuscles have settled the parasite floats to the surface), they soon die in pure oxygen, and also in carbon dioxide. They are very sensitive to high temperatures, becoming motionless in a few hours if kept at fever temperature; they remain alive for the longest time (fourteen days) when kept at 18° to 21° C. They are also very sensitive to the action of water and of salt solutions. Human secretions—saliva, ascitic fluid, urine—are all more or less poisonous to them. All these facts indicate, as do clinical observations, that the spirilla are short-lived (Heydenreich and Kannenberg [38]). Moczutkowsky thought that the increased specific gravity of the blood was the cause of their death, but Albrecht and Wernich (39) attribute it to the action of their own products.

Nothing is known of their existence outside the human body, nor of the method of infection. The other forms of spirilla that we know of are found chiefly in dirty water, and have nothing in common with the spirilla of Obermeier but their name.

Recurrent fever occurs in rural districts amongst the poor and amongst vagabonds, and no doubt insufficiency of food aids the development of the parasite; but neither this nor bad water can be made wholly answerable for the disease, as we know that the infection may spread from person to person. Klebs has suggested that it is spread by household vermin. It is stated that during the fever and directly after the crisis there is a diminution of red corpuscles and an increase of leucocytes (Boeckmann and Heydenreich). It is also stated that large protoplasmic bodies (five times the size of a leucocyte), small motile granules, and fatty degenerated endothelial cells are to be found in the blood, but of these we have no certain knowledge.

C. Filaria sanguinis.

This is known only in the larval condition (Fig. 33). It appears as a slender worm with a rounded head, its average length being 3 mm. and breadth ·14 mm. It is the cause of endemic hæmaturia and chyluria in certain tropical regions (Antilles, India, Zanzibar, Mauritius, Egypt), and was discovered by Patrick Manson (40).

The characteristic of this parasite is that it circulates in the blood only during the sleep of its host (Lancereaux [41]). It is said to be spread by the female mosquito, which sucks it up with the blood, returns to its home on the water, lays eggs, and dies ; the worms then become free, and through the water again enter the human body. By blocking the small blood and lymphatic vessels they cause hæmaturia and chyluria (42). Several other forms closely allied to the above have been described (Manson).

Fig. 33.

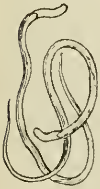
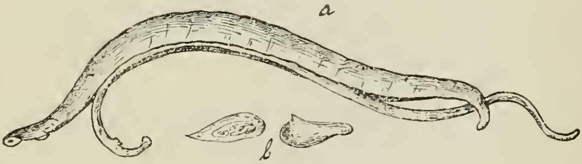


Fig. 34.



D. Distomum hæmatobium (Bilharzia hæmatobia).

The male form of this parasite is from 4 to 15 mm. long, and is provided in the anterior portion with the so-called suctorial pores. In the middle of its body is the gynæcophoric canal in which the female (whose length varies from 15 to 20 mm.) partly lies. The body is approximately cylindrical (43) (Fig. 34). The worm is found chiefly in Egypt, where it is the cause of hæmaturia, especially in man. It is said to be innocuous in apes, cattle, and sheep (44).

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CHAPTER V.

CLINICAL INVESTIGATIONS.

It is customary to divide anæmia into primary and secondary forms according as the cause is known or not; and it is still advisable to adhere to this classification, although cases now considered primary will, no doubt, as our knowledge progresses, be transferred to the secondary class.

A. The Primary Anæmias.

1. *Chlorosis.*—This name is given to a condition which occurs chiefly at the age of puberty, and is characterised by (1) the gradual development of a waxy pallor, with often a greenish tinge; (2) certain changes in the composition of the blood; and (3) loss of function of the organs of digestion and of circulation, without any demonstrable organic disease. It is important to add that, in spite of the malnutrition that obtains (the muscles and bones being usually insufficiently developed), the superficial fat of the body (fat-cushion) is not as a rule diminished.

Hippocrates was acquainted with the clinical features of this disease, but our real knowledge of it dates from Varandal's description published in 1620. Many synonyms have been suggested since then—icterus amantium, morbus virgineus, cachexia virginum, etc. The definition given above suggests that the origin of the disease is in the blood itself, and that the changes in the blood affect the functions of the organs. Now, however, it is generally held that the primary changes occur in the blood-forming organs.

The study of chlorosis in the past has been chiefly clinical, as pathological examination of the organs is rarely possible;

consequently great attention has been paid to the changes that take place in the blood. The first observations on this subject I need mention are those of Prévost, Dumas, and Denys (1), who noticed that the amount of iron in the blood was diminished in this disease.

Andral (2) and Becquerel and Rodier (3) estimated the number of red corpuscles; the former found it uniformly decreased, but the latter found it normal in two out of eight cases. Wunderlich (4) also gives chlorosis as a cause of oligocythæmia. All these results, however, were obtained by the sedimental method, which is unreliable. Duncan (5) was the first to count the corpuscles, and at the same time to estimate the amount of hæmoglobin present. He characterised the condition as one with approximately normal numbers of red corpuscles, but with an abnormally small amount of hæmoglobin. This statement is fully confirmed by Graeber (6). Nevertheless oligocythæmia is often found, as the following table (taken from Reinert [7]) shows:

Name of investigator.	Number of cases investigated.	Number of cases in which the number is four millions and over.	less than four.
Malassez	4	1	3
Sörensen	7	1	6
Hayem	22	7	15
Laache	24	6	18
Halla	1	—	1
Hofer	4	—	4
Toenissen	1	—	1
Stifler	46	19	27
Siegl	32	5	27
Gram	7	5	2
Jacoby	6	—	6
Reinl	5	1	4
Willcocks	7	3	4
Buchanan	3	2	1
Graeber	28	20	8
Oppenheimer	32	24	8
Reinert	18	5	13
Total	247	99	148

We see that oligocythæmia occurs in the majority of cases. Graeber considers it a complication, and as a proof of this quotes the well-known fact that the first sign of convalescence is that the number of corpuscles increases. He infers that the anæmia disappears, and an uncomplicated condition of chlorosis is left. This view of the case is, however, unsatisfactory, in that in the first place oligocythæmia is rather the rule than the exception; secondly, the Duncan condition is found not only in chlorosis but also in other varieties of anæmia; and thirdly, Graeber's illustration is merely a sign of regeneration of the blood, and occurs in all forms of convalescent anæmia, even after traumatic hæmorrhage. These objections are supported in various ways; thus I would refer the reader, in addition to the table above, to sixteen cases of my own (8), in fifteen of which the number of red corpuscles was less than four millions. Stintzing and Gumprecht (9), too, found that out of thirteen cases eight had, at the beginning of treatment, less than three millions. If we add together all the examples we have quoted we find that there is a condition of oligocythæmia in 63 per cent. of the cases of chlorosis. Again, the so-called chlorotic condition of the blood is found in many widely different cases, *e. g.* Reinert found it in two cases of gastric carcinoma, Osterspey in many cases of the same disease, Laache (10) in simple anæmia, and I myself in a large variety of different conditions, of which I give one example.

M. M—, æt. 68. The patient was an old lady of very anæmic appearance, who had suffered for three months from abdominal pain and diarrhœa. She was under observation for three months, during the whole of which time her blood showed the so-called chlorotic condition. She gradually sank, and finally died of facial erysipelas, which she contracted in the hospital.

At the post-mortem examination the mucous membrane of the small intestine was found to be atrophied. The condition of the blood was as follows:

	No. of red corpuscles.	No. of leucocytes.	Hgl. (Fleischl).
Jan. 9 ...	3,050,000 ...	10,000 ...	—
,, 14 ...	3,150,000 ...	5,300 ...	28 %
,, 21 ...	3,700,000 ...	8,100 ...	30 %
Feb. 8 ...	4,500,000 ...	10,400 ...	—
,, 20 ...	4,500,000 ...	8,500 ...	25 %
,, 27 ...	4,230,000 ...	— ...	22 %

Further, Otto (11) demonstrated that during the process of regeneration of the blood, as a rule the corpuscles first increased in number, and afterwards the deficiency of hæmoglobin was made good. In Case 2, in the section on "Therapeutic Influences on the Red Corpuscles" we have a well-marked instance of this, but Case 3 is an exception to this rule. Again, clinically we often see cases in which the number of red corpuscles and the amount of hæmoglobin increase almost equally under the influence of iron, *e. g.* Cases 6, 7, and 9 in the following table:

No.	Name.	Date.	No. of red corpuscles.	Hæmoglobin (Fleischl).
1	B. B.	April 9th, 1889	3.312,000	60
		,, 13th, ,,	4,120,000	60
*2	B. A.	Nov. 20th, 1888	4.380,000	35
		,, 22nd, ,,	4,122,000	40
		,, 24th, ,,	4,200,000	60
		,, 27th, ,,	4.220,000	60
		Dec. 10th, ,,	4.060,000	60
		,, 13th, ,,	3,816,000	58
		,, 17th, ,,	3,887,000	72
		Jan. 3rd, 1889	3,750,000	72
*3	B. M.	March 7th, 1889	1,865,000	23
		,, 10th, ,,	1,700,000	25
		,, 21st, ,,	3,450,000	30
		,, 29th, ,,	4,260.000	30
		April 3rd, ,,	5.240.000	50
		,, 5th, ,,	4,912.000	60
4	S. T.	July 3rd, ,,	3,080,000	30
	D. C.	Feb. 5th, ,,	3,600.000	30
5	W. R.	Dec. 31st, 1888	2.830,000	40
*6	N. E.	Jan. 29th, ,,	1,933.000	50
		Feb. 5th, ,,	—	60
		,, 12th, ,,	3.592,000	75
		,, 26th, ,,	3,448,000	72
7	R. F.	Dec. 9th, ,,	2.683.000	42
		,, 16th, ,,	3,420,000	50
8	B. M.	Nov. 14th, ,,	2,183.000	40
9	R. B.	,, 9th, ,,	1,750,000	30
		,, 15th, ,,	2,360.000	30
		,, 17th, ,,	2,220,000	35
		,, 24th, ,,	2,640,000	25
		Dec. 5th, ,,	3.000,000	35
		,, 10th, ,,	4,140,000	45
		,, 16th, ,,	3,300,000	55
*10	K. K.	Jan. 21st, 1889	3.200.000	45
		,, 23rd, ,,	2,876,000	45
		,, 26th, ,,	2,904.000	48
		Feb. 1st, ,,	2.856,000	45
		,, 10th, ,,	3,860,000	60

* Treated with iron.

No.	Name.	Date.	No. of red corpuscles.	Hæmoglobin (Fleischl).
*11	H. A. .	Oct. 15th, 1888 .	2,600.000	20
		,, 19th, ,, .	2,800,000	20
		,, 23rd, ,, .	2,925,000	—
		,, 28th, ,, .	3,347,000	30
		Nov. 1st. ,, .	4,240,000	45
		,, 12th, ,, .	—	48
12	Z. A. .	Aug. 12th, 1889 .	1.190,000	27
		,, 10th, ,, .	2,570,000	35
		,, 16th, ,, .	3,110,000	48
		,, 23rd, ,, .	3,010,000	57
		,, 30th, ,, .	3,140,000	55
*13	R. B. .	Oct. 7th, 1888 .	3,190,000	28
		,, 10th, ,, .	3,576,000	27
		,, 15th, ,, .	3,360,000	30
		,, 18th. ,, .	3·950,000	33
		,, 21st, ,, .	4,100,000	36
*14	P. M. .	Dec. 21st, 1889 .	2.500,000	28
		Jan. 3rd, 1890 .	2,140.000	43
		,, 16th, ,, .	3·340.000	45
15	R. F. .	March 10th, 1889 .	1.760,000	25

* Treated with iron.

Hence we are bound to come to the conclusion that the so-called chlorotic condition of the blood is *not* characteristic of chlorosis. It is true that very often the average amount of hæmoglobin in a red corpuscle is less than normal; but this is also true for other forms of anæmia.

Other abnormalities, none of which are characteristic, may be found in chlorotic blood in addition to this oligochrômæmia. We may, *e. g.*, see nucleated red corpuscles sometimes in large numbers (blood crises—Neudörfer [12]); whilst microcytes, poikilocytes, megaloblasts, and the signs of degeneration described by Maragliano and Castellino may all be found in severe cases (Hammerschlag [13]).

The *density* of the blood is usually below the normal. Graeber and Drouin (14) found the *alkalinity* increased, but Kraus (15) proved that it was normal. Steindler and myself (16), using my coagulation method (17), found the total alkali in the blood = ·208 per cent. NaOH, in the serum of defibrinated blood = ·145 per cent., and in the serum of spontaneously coagulated blood = ·192 per cent., *i. e.* normal values. In two cases I found the isotonic co-efficient very low = ·38 and ·4 per cent. NaCl, as it is in cases of jaundice.

There is seldom any appreciable abnormality in the leucocytes or platelets, either in quantity or quality. Hammerschlag (13) has noted the presence of marrow cells in severe cases.

I append a table taken from Becquerel and Rodier, which gives the average of six cases, to illustrate the chemical constitution of the blood in chlorosis. The excess of water and the deficiency of hæmoglobin are marked whether oligocythæmia is present or not.

Density of the blood	1045·8
,, ,, serum	1028·1
Water	828·2
Corpuscles	86·0
Albumen	72·1
Fibrin	3·4
Extractives and salts	8·8
Fats	1·503
Seroline	variable
Cerebrin	·541
Cholesterin	·054
Soap	·888
In 1000 g. of calcined blood :	
Sodium chloride	3·1
Soluble salts	2·3
Phosphates	0·441
Iron	0·319

A comparison with the composition of normal blood shows an increase of water, fibrin, albumen, and phosphates, and a diminution of corpuscles and sodium chloride. The density of the blood is lowered and that of the serum slightly increased.

Biernacki (18) has made accurate analyses of the dry residue of chlorotic blood. He found an increase of water, sodium, and chlorides, and a diminution of potassium, whilst the quantity of iron was sometimes normal and sometimes diminished. The iron was actually increased in some cases where the amount of albumen was normal. Biernacki comes to the conclusion that in chlorosis the corpuscles are characterised, not by deficiency of hæmoglobin, but by deficiency of albumens.

We see, then, that a diagnosis of chlorosis cannot be made from an examination of the blood alone. It may be that the condition is the result of ætiological causes of different nature. If it is really a special disease, different from other forms of anæmia, there must be some broad mark of distinction, such as the absence of signs of degeneration in the red corpuscles (v. Noorden [19]).

It has often been observed that in this disease there is no excess of hydrobilirubin in the urine ; this is in marked contrast to many other clinical forms of primary anæmia, but not to all, *e. g.* traumatic anæmia.

The exciting cause of the blood changes in chlorosis is unknown. The deficiency of the red cells must be due to a diminished formation of new cells, as the signs of degeneration of these cells are so scanty. This might be the result of many different causes. v. Noorden (20) and Lippman Wulf (21) have shown that it is not due to errors of digestion nor to abnormal absorption of food ; this is in accordance with the fact that starvation does not cause either oligochromæmia or oligocythæmia. I estimated the amounts of fat and of nitrogen absorbed from food and found them to be normal.

2. *Simple primary anæmia.*—This name is given to those cases of anæmia which are not secondary to other diseases, and which are, as a rule, readily amenable to treatment.

It is only in typical cases that we can draw a sharp line of distinction between this condition and chlorosis or pernicious anæmia. Unfavourable conditions of existence are an important ætiological factor in the disease, but at present we do not know the particular influences that affect the composition of the blood.

In these cases the most important point clinically is to decide whether destruction of red corpuscles is going on or not. This would be shown by the Maragliano signs of degeneration, by hydrobilirubinuria, or by jaundice. From this point of view the cases fall into two groups, which are to be distinguished from one another, both as regards prognosis and treatment. The prognosis is favourable if there is no increased destruction of red corpuscles. Even if the oligocythæmia is severe the administration of iron or arsenic with suitable food in such cases soon restores the blood to its normal condition; but, if there are signs of destruction of the red corpuscles, the prognosis depends upon its amount, and the degree of the oligocythæmia present. The rule as regards the condition of the blood is, that the diminution of red corpuscles and the hæmoglobin are proportional (Graeber [6]). Exceptions to this rule, however, occur in both directions. Laache (16) showed that the average amount of hæmoglobin in a corpuscle might be below the normal; sometimes also we find it greater than normal.

K. A—, widow. Case of malnutrition. Anæmia with no organic lesion.

	Number of red corpuscles.	Hgl. (Fleischl) per cent.
June 4th	306,000	18
,, 8th	312,000	18
,, 17th	529,000	23
,, 23rd	1,280,000	28
,, 27th	1,300,000	35
July 4th	2,480,000	50
,, 12th	1,980,000	45
,, 15th	1,660,000	48
Aug. 2nd	2,088,000	45
,, 9th	2,464,000	55
,, 16th	2,230,000	53
Discharged, and readmitted October 22nd.		
Oct. 23rd	700,000	26
,, 28th	680,000	25
Nov. 3rd	860,000	30
,, 6th	1,120,000	30
,, 10th	1,700,000	32
,, 18th	2,800,000	55
,, 23rd	2,680,000	65
,, 30th	3,160,000	65
Dec. 6th	4,280,000	65

The blood showed marked signs of hæmolysis, and there was slight jaundice. The relation of the diminution of hæmoglobin to that of red corpuscles was not uniform; sometimes they were diminished in proportion, but often the decrease of one or other was excessive.

We see that the diminution of the hæmoglobin and the decrease of the number of red corpuscles are not always proportional. This has been noted by others, including Hayem (22). Normoblasts, micro- and macrocytes, poikilocytes and megaloblasts may also appear in the blood. These are found in all severe anæmias, and are therefore not characteristic of any special form. In chronic cases the leucocytes are generally normal in quantity and quality. The platelets are often increased in number, especially in severe cases.

The specific gravity of the blood falls, its diminution being approximately proportional to the diminution of the hæmoglobin. The alkalinity was found by v. Jaksch to be somewhat below the normal. I found the alkalinity of the serum, obtained by centrifugalisation by my own method, = ·184 per cent NaOH, whereas the normal is from ·224 to 38 per cent.

Biernacki (18) gives the following example of the chemical composition of the blood:

Number of red corpuscles	2,845,000
,, leucocytes	7500
Hæmoglobin	65 per cent.
In 100 g. of the blood:	
Dry residue	17·83
NaCl + KCl	·632
K_2O	·142
Na_2O	·216
Fe	·0406

The dry residue with the potassium and iron are diminished, but the sodium and chlorine are normal.

The following table shows the division of nitrogen, chlorine, and water between the serum and the corpuscles, together with the volumes of the latter:

M. K—, æt. 55. Anæmia of unknown origin.

Number of red corpuscles	1,227,000
,, leucocytes	6,200
Hæmoglobin	25 per cent.

Density of the blood	1031	
,, serum	1021	
Isotonic value of the corpuscles	·54	NaCl.
N_2 in the blood	1·48	vol. per cent.
,, serum	0·852	,, ,,
NaCl in blood	0·897	,, ,,
,, serum	0·819	,, ,,
Dry residue of blood	11·56	,, ,,
,, serum	7·33	,, ,,
Vol. of serum	92·41	per cent. of total blood.
,, corpuscles	7·59	per cent. of total blood.
Vol. of a corpuscle	61·7	c.mm. C.
Weight ,,	71·2	mg. ,,
Sp. wt. ,,	1·153	,, ,,
N_2 in ,,	56·1	,, ,,
NaCl ,,	11·4	,, ,,
Dry subst. ,,	39·0	,, ,,
Water ,,	32·2	,, ,,

This case shows the following differences from normal blood:

(*a*) In the blood—the density, nitrogen, and dry residue are diminished, the salt and water are increased.

(*b*) In the serum—the density, nitrogen, and dry residue are also diminished, and the salt and water increased.

(*c*) The isotonic co-efficient of the corpuscles is greater than normal; that is to say, their resistance to water is less than that of normal corpuscles.

As regards the individual red corpuscles, the volume, weight, and specific gravity are not appreciably increased, but there is a marked increase in the amount of nitrogen, and still more in the amount of salt.

Biernacki asserts that an increase of sodium chloride occurs in all varieties of hydræmia.

3. *Progressive pernicious anæmia.*—This name, given by Biermer (23), indicates a condition of severe anæmia which, in spite of all therapeutic measures, progresses without abatement and ends in death (Eichhorst [24]). No organic

disease can be found to account for the anæmia. This conception of the disease has, however, of late been changed. In some cases which present a similar clinical picture the cause of the disease is known, *e. g.* intestinal parasites. Hence some modern authors have divided the disease into two classes:—(1) primary or idiopathic, in which the cause is unknown; (2) secondary, deuteropathic or symptomatic. If, however, we hold that the condition described by Biermer really exists, it would seem reasonable to limit the term idiopathic anæmia to those cases in which no primary cause can be found, although no doubt with the increase of our knowledge these will become fewer and fewer.

The blood-changes in pernicious anæmia are not characteristic; the same changes are found in all forms of severe anæmia. Formerly several of these changes were in turn considered to be diagnostic of the disease, *e. g.* Quincke (25) considered poikilocytosis as such, and Laache (10) and Kahler (26) thought that they had found a characteristic alteration in the relative richness in hæmoglobin, as compared with the diminution of the red corpuscles. Quincke's idea was soon corrected, but the latter view is still found in text-books, although, as a matter of fact, this relative increase of hæmoglobin occurs in nearly all cases of severe oligocythæmia.

The number of red corpuscles is excessively diminished. Their contour becomes irregular, and poikilocytes appear, frequently microcytes and megalocytes, and, if there is any degree of regeneration, the nucleated cells that go by the names of normoblasts, megaloblasts, and poikiloblasts, can be seen. The hæmoglobin in these cells is sometimes increased, but may be normal in amount. As death approaches the number of red cells usually decreases.

V. K—, æt. 35. Grave anæmia of unknown cause. Jaundice.

	Red corpuscles.	Hæmoglobin per cent.
March 12th	350,000	20
,, 13th	320,000	22
,, 16th	280,000	18
,, 19th	Death	—

The lowest number yet recorded is 143,000, in a case of Quincke's. The number of leucocytes is not increased. The platelets are increased in number, and often lie in heaps in the preparation.

None of these signs distinguish pernicious anæmia from other forms of severe anæmia. One point, however, is of importance in this respect, viz. the rapid destruction of the red corpuscles, shown by excessive signs of degeneration, by hydrobilirubinuria, and by jaundice. In this way we are able to eliminate many forms of severe anæmia, *e.g.* chlorosis.

Quincke, and after him Scott (27) and Hopkins (28), found deposits of iron in the liver in cases of true pernicious anæmia. This has been confirmed by many others, and was explained by Ponfick, who showed that when red cells are destroyed the hæmoglobin is deposited in the liver, and the stroma in the spleen.

4. *Leukæmia.*—This is a disease which usually runs a chronic course, and is characterised by certain changes in the lymphatic system, and by a peculiar alteration in the constitution of the blood whereby the number of leucocytes is increased, often to an immense degree, while that of red corpuscles is but slightly diminished. Virchow (29), in 1845, was the first to recognise it as a special disease. Others (Piorry, Bennet, and Rokitansky) had noticed these changes, but had considered them to be of a pyæmic nature. According to Virchow the primary changes are those in the spleen and lymphatic glands, those in the blood being secondary. The latter, he thinks, are caused partly by interference with the development of the red corpuscles in the blood-forming organs, and partly by the passage of certain chemical substances into the blood.

This general view of leukæmia was accepted, at any rate in part, by the majority of authors.

It was not until Ehrlich introduced his staining methods that attention was directed towards the changes in the blood, the previous investigations being directed towards the nature of the changes in the organs. Virchow, Mosler (30), Klebs (31), and others had, indeed, given a correct general description of the blood-changes, but a detailed account of the character of the abnormal elements was in those days impossible. Virchow divided the cases into two classes—splenæmia and lymphæmia; in the former large white cells were said to pass into the blood in increased numbers from the spleen, in the latter smaller ones from the lymphatic glands. This distinction still holds good, although it is now considered probable that these large white cells arise in the bone-marrow and not in the spleen, and that, therefore, myelæmia would be a more suitable name than splenæmia. The number of red corpuscles is, according to the majority of investigators, diminished in this disease. The diminution is seldom excessive, but is rarely absent (Quincke, Litten, Waldstein). The quality of the red corpuscles is also altered. There are signs of degeneration poikilocytes and the endolobular necrotic changes described by Maragliano. Nucleated red corpuscles are often observed, especially in the splenic and medullary forms. In lymphatic leukæmia nucleated red corpuscles are rarely or never seen (Wertheim [32]).

The number of leucocytes is always increased, and sometimes to an enormous degree; so that 500,000 per c.mm. is not an uncommon number. During the course of the disease the number may undergo considerable variations. These may be due to therapeutic influences, but may also be due to quite different causes; *e. g.* an acute infectious disease may, during the course of leukæmia, cause a diminution of the number of cells previously increased, and at the same time involution of the diseased organs (33—38).

The character of the cells that are increased in number varies according to the type of disease. If we examine under the microscope a drop of blood taken from a case of spleno-medullary leukæmia, we find, in addition to the finely granulated cells, with one or more nuclei, those coarsely granulated cells to which the name eosinophile was given by Ehrlich. These coarse granules were originally thought to be of a fatty nature. Litten (39) found that they were stained by osmic acid; Müller (40) confirmed this, but doubted whether they were fatty, as it is not certain that everything is fat that stains with osmic acid. From other investigations (Weiss [41], Posner [42]) it seems probable that the granules contain albumens. In addition to these forms we also find marrow cells, which are absent in normal blood. Mosler was the first to demonstrate their presence in the blood of leukæmia. He punctured the sternum, and found the same cells in the fluid extracted from the bone, thus showing that the bone-marrow was the probable source of the cells. This observation has been confirmed, and Müller (43) has recently shown that these cells are identical with Cornil's "cellules medullaires." They are characterised by their large size and by the poverty of their nuclei in chromatin. They show no amœboid movements (Löwit [44]) on a warmed object slide. Until recently it was doubted whether these cells appeared in any disease except leukæmia; but of late they have been found in many other conditions by Weiss (45), Zappert (46), Loos (47), and Neusser (48). Zappert found them in skin diseases, and Neusser states that they occur in uræmia.

We also find mononuclear lymphocytes and neutrophile cells, which may be polynuclear, or may have a single nucleus of the so-called transition form. The mononuclear lymphocytes have, as a rule, no specific granulation, but occasionally we come across some that have granules which are basophile. It has been maintained (amongst others by Loos) that basophile cells appear in human blood only in spleno-medullary leukæmia, but even in this disease they are seldom seen. They have also been found in cases of congenital syphilis. All the white cells do not share equally in the leucocytosis of spleno-medullary leukæmia. We always find a preponderance of the mononuclear cells. Löwit (44) estimated that 84 per cent. of the white corpuscles were mononuclear, and 16 per cent. transition and polynuclear cells—just the reverse of the normal relations. If we classify the leucocytes according to their staining properties, we do not find so uniform a change. It is true that the eosinophile cells are always increased in number, but their percentage as compared with the other white cells is not increased (Müller and Rieder [49], Zappert). Zappert examined ten cases, and found that the eosinophile cells formed 8 per cent. of the total number of leucocytes. The percentage in normal cases is often greater. In two cases of my own I found the percentages 4·4 and 6·2.

The great majority of the cells are neutrophile, a few have, as we have seen, basophile granules, and there are a few isolated mast cells. An exception to this preponderance of mononuclear cells only occurs when the disease is complicated by an inflammatory leucocytosis.

Another peculiarity of the blood in this disease is the appearance of mitotic division in the nuclei of the white cells. This has been described by Fleming (50), Hayem (51), Pruss (52), Spronk (53), and others; but Löwit (54), in accordance with his theory of blood-formation, holds that the cells in which it appears are not leucocytes, but the antecedents of the red corpuscles (erythroblasts).

Pruss appears to have been the only observer who has estimated the number of blood-platelets in leukæmia. He found it appreciably increased, the average being two millions per mm., whereas in normal cases it is only ·5 million.

Charcot-Leyden (55, 56) crystals have been found repeatedly in leukæmic blood during life (57—61). Westphal (61) punctured the spleen in two cases of leukæmia and found these crystals; he concludes that they are formed in the spleen. Others think they are produced from the plasma by crystallisation. Charcot and Vulpian described them as octahedra, but more recently Cohn (62) has described them as hexagonal pyramids. According to Schreiner (63) they are composed of a combination of phosphorus with an organic base. They occur normally in bone-marrow (Neumann [57]). v. Jaksch (64) and myself have never succeeded in finding these crystals in leukæmic blood.

There are many differences of opinion with regard to the pathology of the disease. The first question is whether the increase of cells is due to greater production or less destruction (or less change into other forms); the second, whether the primary change is in the blood or in the organs. As we have seen, Virchow considers the disease of the organs to be primary, and to cause the increase of white and the diminution of red corpuscles; that is, he thinks leukæmia is not a blood disease strictly speaking, but a disease of the lymphatic system. Neumann's discovery—that the bone-marrow participated in leukæmic processes—affected Virchow's theory, in that it was necessary to add a myelogenous or medullary form of leukæmia. Most authors agree in placing the primary site of leukæmia in the blood-forming organs, but a few consider it a primary blood disease. Biesiadecki (65) thinks the transformation of colourless into red cells is hindered; Kottmann (66) holds that the leucocytes enter the blood-vessels in normal numbers and there proliferate; and Löwit (67) that there is an obstruction to the development of mononuclear into polynuclear cells, caused by some change in the protoplasm of the cells, which is marked by their loss of amœboid movements. Virchow's view has been generally adopted, especially since the identity of the marrow cells in the blood and of those in the marrow has been established. We have, according to Wertheim, an excessive formation in the blood-forming organs of colourless mother-cells, in which the development into white and red corpuscles does not take place normally. Wertheim asserts that it is owing to this increased blood-formation that the anæmia which occurs is usually slight, and may even be absent. H. F. Müller, too, considers the primary cause of leukæmia to be a hyperplasia of the blood-forming organs, and that in this way proliferation of leucocytes is brought about.

Many attempts have been made to trace some ætiological connection between leukæmia and such influences as heredity (68), pregnancy (69), conditions of nutrition, intermittent fever (70), tuberculosis, syphilis, acute infectious diseases (71), and pernicious anæmia (72); but these were very obscure, and at the same time gave no explanation of the direct cause of the disease. Attempts to add leukæmia to the list of acute infectious diseases, by means of culture experiments (Krebs [73], Osterwald [74], Roux [75], Pawlowski [76]), have also failed. Consequently we are now almost reduced to the conception of leukæmia as a process analogous to the malignant neoplasms. This, however, does not make the ætiology any clearer (Bard [77], Gilbert [78]).

Lymphatic leukæmia differs somewhat from the lienomedullary form and, as it occurs less frequently, is still less understood. The number of red corpuscles is in this form, also, usually somewhat diminished. Hayem (79) found 3·72 millions per c.mm., Müller (80) 2·55, and the author 3·5 millions. The paucity of nucleated red cells is striking; either there are merely one or two isolated ones, or they are totally absent. It is universally admitted that the greater part of the colourless cells is composed of small mononuclear lymphocytes. Comparatively few cells are polynuclear or polymorphous, while eosinophile cells are rare. Marrow cells are few and isolated. Mitosis of the leucocytes is not seen, and is considerably less in the blood-forming organs than in the other form of the disease. The differences between pure lymphatic leukæmia and the lieno-medullary form are so great that it is a question whether the two are akin. Wertheim thinks that there is no similarity between the two processes; Müller, on the other hand, considers that they represent the same pathological process which, in the lymphatic form, takes place in the lymphatic system; that all the different varieties of leukæmia may merge into one another, and so on.

The leukæmic process seems sometimes to be confined to the lymphatic glands. Whether this is a true leukæmia or not remains to be proved. In my cases the condition of the blood rather resembled that of lympho-sarcoma, the only difference being in the amount of leucocytosis. In lympho-sarcoma the number of leucocytes is seldom as great as in lymphatic leukæmia, but the difference is not sufficient to be of clinical value.

The differential diagnosis from other diseases is often difficult in all forms of leukæmia. In many cases a microscopic examination is sufficient, but there are cases in which the distinction from pathological leucocytosis is doubtful. Formerly the relative proportion of the white and red corpuscles was thought to be a decisive point, *e. g.* a ratio of 1 to 50, or 1 to 20, was said to be diagnostic of leukæmia (Huss [81]). Such might, however, exist in a case of intense leucocytosis, especially in an anæmic individual (Eisenlohr's case of carcinoma showed a ratio of 1 to 50). A numerical criterion, too, does not indicate any difference in the pathological process. Other infallible criteria were sought for, especially after the development of Ehrlich's methods. Ehrlich's criterion (92)—the apparent increase of the eosinophile cells—does not hold good, and the reliability of the diagnostic sign more recently proposed by Müller, viz. the presence of marrow cells, has been of late questioned. Hence it appears there is no one certain diagnostic sign of leukæmia. In making a diagnosis, the most important point is the preponderance of mononuclear cells, and next to this the appearance of marrow cells. This may be sufficient for spleno-medullary leukæmia, but it does not serve to distinguish lymphatic leukæmia from sarcoma. Excessive leucocytosis in sarcoma (which may be of the mononuclear form), and a moderate lymphatic leukæmia, cannot be distinguished from one another by an examination of the blood alone.

As regards the chemical composition of the blood in leukæmia, I have already called attention to the presence (Ch. III, Sec. 2) of abnormal albumens; Salkowski (83) and Pruss have, in addition, found a large amount of lecithin.

The composition of the dry residue is shown in the table in the same section. Samson and Himmelstjerna (84) noticed that the time of coagulation in leukæmic blood was longer than normal. This was confirmed by Freund, who thought the explanation lay in the fact that the peptones in leukæmic blood held the calcium phosphate in solution, and that therefore coagulation was delayed. Fano's observation, that the introduction of carbonic dioxide into blood containing peptone would cause coagulation, induced Rywosch and Berggrün to examine the effect of carbon dioxide on leukæmic blood. They found that coagulation took place more quickly than when the blood was left to itself, whereas healthy blood gave exactly opposite results. The amount of fibrin, as compared with the amount formed in spontaneous coagulation, was also increased after the introduction of carbon dioxide.

Leukæmia acuta and acutissima.—These names are applied to those rare cases in which the leukæmic changes run a rapid course. The published cases of this nature have been collected by Ebstein (86) and Kossler (87), and are about thirty-five in number. Their duration varies from six days to nine weeks. A large degree of leucocytosis invariably obtained, but sometimes it appeared only just before death (88—91). In many of the cases changes of a leukæmic nature were found in the blood-forming organs, so that there can hardly be any doubt that an acute form of leukæmia does exist. With regard to the changes in the blood, a sufficient number of investigations has not yet been made. According to Leyden (88), Greiwe (89), and Kossler, the acute cases may, like the chronic, be divided into splenic, spleno-medullary, and lymphatic forms. Eichhorst (92) describes a pure splenic variety, Leyden and Kossler a lieno-myelogenous form, and Kossler and Greiwe a lymphatic form. Kossler remarks in reference to his first case, "Hardly any neutrophile polymorphous leucocytes are seen, but only myelocytes; no lymphocytes, and no nucleated red corpuscles." The amount of leucocytosis was 1·60. This was the case of a female aged twenty-seven, who died after an illness lasting seven days. In Kossler's second case (lymphatic form) and in Greiwe's case the increase of leucocytes was composed of small lymphocytes. In all the cases there was some degree of oligocythæmia, and in some of them (Gottlieb [93], Waldstein [94]) severe anæmia was at first the chief symptom, and it was only shortly before death that an enormous increase of leucocytes was observed. The oligocythæmia was not very great (3·273—2·125 millions red corpuscles), and one source of it was, no doubt, hæmorrhage.

Hæmorrhage may account for a leucocytosis up to 30,000, but it certainly cannot account for one of 300,000 or more, which was frequently noted.

It is not easy to decide whether the cases described as acute leukæmia form a distinct type of disease or not, especially as some of the older cases seem to me not to have been leukæmia at all, but leucocytosis of high degree (*e. g.* the case of Schede and Stahl [95]).

In other cases the disease ran quite a dissimilar course. In one the course was rapid, resembling that of acute poisoning; in another, severe anæmia gradually developed, and leucocytosis was suddenly superimposed; and a third case resembled an acute infectious fever. No doubt there were leukæmic changes in many of the cases, but we do not know for certain that some severe infections or intoxications may not produce changes in the blood similar to those in leukæmia.

Recently Fraenkel ('Deutsch. med. Woch.,' 1895, Nos. 39

—43) has published a *résumé* of ten cases of acute leukæmia. He finds the characteristic of the blood in these to be lymphæmia, the increase of cells being composed almost entirely of young mononuclear lymphocytes, the nuclei of which were extraordinarily poor in chromatin, and were sometimes of the polymorphous variety, whilst the cell body contained granulations that were sometimes basophile, but never neutrophile. Eosinophile cells were very rare. Mitosis of the nuclei of the leucocytes and nucleated red corpuscles was occasionally found.

5. *Pseudo-leukæmia.**—The majority of cases to which we apply the name of leukæmia form, no doubt, one specific type of disease; but this cannot be said of the so-called pseudo-leukæmia. Conditions are included under this heading which are clinically and anatomically different, but which we are unable at present to properly classify.

In 1823 Hodgkin described a type of disease that up to that time had not been observed. This was a sort of general cachexia, running a chronic course, and associated with enlargement of the spleen and lymphatic glands.

In 1845 Virchow described the leukæmic processes, and later Cohnheim (96) called attention to a case which strongly resembled leukæmia, but which differed in the character of the blood, so that there seemed to be two different pathological processes.

Since this time so many apparently different forms of disease have been classed together under the heading of pseudo-leukæmia, or one of its synonyms, that it is doubtful whether we are justified in considering it as a distinct type of disease. Again, cases which at first are placed under this heading subsequently turn out to belong to some other class, *e. g.* tubercle (97) or leukæmia. Often, too, the glandular swellings appear to be true tumours (98). Fraenkel (100) maintains that these swellings, when not tubercular, syphilitic, or leukæmic, are always true tumours; but Billroth (99) made a distinction between malignant lymphoma and sarcoma, viz. that in the former the glands do not become fused together. Kundrat (101) attempts to distinguish lymphosarcoma from true sarcoma, but describes the existence of transitional forms between the former and pseudo-leukæmic tumours.

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* *Syn.—Anæmia lymphatica* (Wilks), *Cachexie sans leucémie* (Bonfils), *Adenie* (Trousseau), *Anæmia splenica* (Griesinger), *Malignant lymphosarcoma* (Langhans), *Malignant lymphoma* (Billroth), *Desmoid carcinoma* (R. Schulz), and Hodgkin's disease.

Other authors (102 to 107) consider the disease to be a specific infection, but clinically it differs from an infectious fever as much as it does from malignant disease. Again, the micro-organisms found by these observers are anything but uniform in character.

I do not think that we are justified at present in considering pseudo-leukæmia as a specific pathological condition. It seems to include cases of true tumours, inflammatory swellings, and perhaps also true leukæmic swellings. In the last condition the blood probably takes on the characteristics of leukæmia in the later stages of the disease (Mosler [108], Westphal [109], and Rothe [110]). It is not surprising under these circumstances that there are no characteristic changes in the blood. The most contradictory results have been published, especially as regards the leucocytes. The number of red corpuscles and the amount of hæmoglobin are in general equally diminished. The number of leucocytes is sometimes normal, sometimes diminished, but usually increased. The blood varies according to the quality of the tumours. I found in two cases of "anæmia splenica" that the number of leucocytes was normal, and the blood of a chlorotic character. The cases associated with glandular enlargements generally show leucocytosis, though often of moderate degree.

The quality of the additional cells varies. If the increase consists of polymorphous cells, it shows that the character of the glandular swellings is probably inflammatory. If the small lymphocytes preponderate, the case resembles that of sarcoma of the lymphatic glands. We get a corresponding increase of leucocytes if fever is present (111 to 113).

Pseudo-leukæmia may, in rare cases, run a very rapid course—a condition we may call acute pseudo-leukæmia. Here, too, different pathological processes are described under the same name. Ebstein (86), *e. g.*, describes a case as such in which a hæmorrhagic condition, together with fever of moderate degree, was the sequel of a dental abscess.

Lannois and Groux (114) and Lannois and Courmont (115) made cultivations of micro-organisms from the glands in their cases, and found the *Staphylococcus pyogenes aureus* and the *Streptococcus pyogenes* respectively.

It seems to me that some of these cases belong rather to the pyæmic class, but other cases, *e. g.* those of Müller (116) and Kossler (87), where inflammatory processes in the glands were excluded, bear a close clinical resemblance to the rest. In all the cases pallor, oligocythæmia, reduction of hæmoglobin, slight leucocytosis, hæmorrhages, enlargement of the spleen and lymphatic glands, moderate fever, and sometimes jaundice were present. All these symptoms may be due to a great variety of causes, for instance, so-called acute sarcomatosis (Fagge [117]) and chronic pyæmia. The majority of cases, however, have rather the character of an acute infectious fever.

B. The Secondary Anæmias.

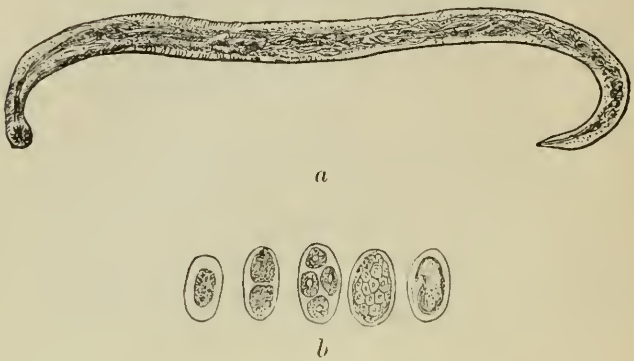
Under this heading we include all those forms of oligocythæmia that are caused by lesions of known nature. There is, of course, no marked line of distinction between these and primary anæmias, especially as we are usually doubtful as to how they produce anæmia—*e. g.* syphilis. We shall consider these under the following headings:

1. Anæmias caused by intestinal parasites.
2. ,, following chronic infectious diseases.
3. ,, ,, malignant disease.

1. *Anæmias caused by Intestinal Parasites.*

(*a*) *Anchylostomum duodenale* (*Dochmius sive Strongylus duodenalis*) (group of Nematodes).—The body of this worm is cylindrical, and its head conical. The latter is provided with a jaw-like mouth-capsule, with two powerful tenacula. The male is 6 to 10 mm. in length, and has at the hinder end of the body a tri-lobate bursa and two slender spiculæ. The tail of the female is pointed, and the vulva lies behind the centre of the body. The ova (Fig. 35, *b*) are oval and smooth on the surface; they have a thin capsule and double contour. Their average length is 65·2 μ and breadth 39·12 μ.

FIG. 35.



They develop primarily without a host, in muddy water or damp clay, and then reach the human body.

Adult worms gorged with blood and eggs in different stages of segmentation have been found in the fæces of an infected individual. The existence of the parasite in Brazil and in the East, especially in the mud of the Nile, has been known for many years. Recently it has been found in Europe, viz. in Italy (118 to 123), and in Switzerland amongst the Italians working on the St. Gothard tunnel (124 to 126). It was spread over other parts of Europe probably by the Italians.

In Germany it was first found by Leichtenstern (127) in the fæces of brick-workers in Cologne, but has since been found by a great many observers (128 to 140) in different districts, chiefly amongst those digging up earth.

Infection usually takes place by the mouth (141). Reproduction does not occur in the intestine. The eggs are generally passed in the fæces while in the "yolk-furrow" stage; they develop rapidly if they fall on moist ground.

The adult parasites lie in the duodenum, jejunum, and ileum, and live on the blood of the host. It is said that they take their nourishment chiefly from the plasma, and consequently abstract more blood than is necessary for their nutrition.

The number of parasites in one host varies—*e. g.* Leichtenstern found in one case post mortem only 24 in the whole intestine, whilst Monighetti found 150 in the fæces during two days after the administration of 10 gr. of Ext. Filic. Mar. Faciola (142) found 500 in another case after death.

The life of a parasite is comparatively long. Leichtenstern estimates it at five years. According to this observer the females predominate in the human body in the proportion of twenty-four to ten.

Griesinger (143) asserts that blood may continue to flow from the wounds made, after the suction of the parasite has ceased. Whether these continued small losses of blood are sufficient to cause the high degree of oligocythæmia that often occurs is not certain. Lussana (144) thinks that a toxic substance, having a hæmolytic action, is also produced. With regard to the condition of the blood, Zappert finds an abnormal relation of the number of red corpuscles to the amount of hæmoglobin, *e. g.*—

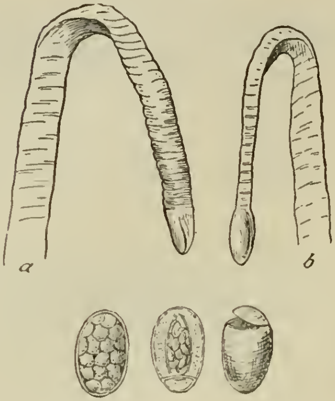
4·35	million	red corpuscles to	50	per cent.	hæmoglobin.
2·496	,,	,,	25	,,	,,
4·384	,,	,,	40	,,	,,
3·204	,,	,,	40	,,	,,
4·272	,,	,,	30	,,	,,

He showed that the loss of hæmoglobin was proportionately greater than that of red corpuscles, *i. e.* the so-called chlorotic condition of the blood. This, in my opinion, is merely a sign of regeneration. The number of leucocytes is generally normal—a fact that weighs against Lussana's suggestion, for in other forms of toxic action there is, as a rule, leucocytosis.

Müller and Rieder (145) have found the number of the eosinophile cells increased, but Zappert says that this is not always the case.

(*b*) *Bothriocephalus latus* (Cestodes).—This is a tapeworm 6 to 8 m. in length (Fig. 36), possessing possibly several thousand segments. These segments are narrow (at the most 3·5 mm. in width); the head (2 mm. by 1) is bean-shaped, being somewhat flattened, and has on each side a suctorial pore. In front the body is narrow, the segments increasing in length and breadth towards the middle, and diminishing again towards the tail. The whole presents a flat ribbon-like appearance. The mature segments show a characteristic stellate appearance when full of eggs, which is caused by the retiform uterus. These eggs are oval (·07 by ·045 mm.) and covered by a brown shell, which at one pole has a sort of lid. The eggs contain fairly large, light-coloured protoplasmic balls. The appearance of and damage caused by this worm have been matters of recent study in the Russian and Prussian provinces which border on the Baltic. In Europe the worm has been found in Switzerland, Sweden, Germany, and Italy. It is common (Baelz [146]) in Japan. Numerous observations on the subject have been published (147 to 160), the most recent being a monograph by Schaumann (161).

FIG. 36.



The parasite may cause the gravest degree of anæmia with all the consequent changes in the blood, but when it has been got rid of, health, as a rule, is speedily regained. Lichtheim (150) quotes a cases in which the number of red corpuscles was only 500,000 and the amount of hæmoglobin 20 per cent.; after death six tapeworms were found in the intestine. Schapiro (155) gives a case with 837,000 red cells; a vermicide was administered, and the number rose to 3,000,000 in twenty-three days.

In a case of Podwyssozky's (156) the number rose from 1·183 to 4·056 millions after the worm was expelled, and in one of Westphalen's (162) from 840,000 to 3,636,000.

Askanazy (160) gives the following case bearing upon the relations of the red corpuscles and the hæmoglobin:

On admission hæmoglobin 30 per cent.; number of red corpuscles 1·2 millions.

After expulsion.	Hæmoglobin.	No. of red corpuscles.
8 days	30 per cent.	1·2 millions.
16 ,,	35 ,,	2·14 ,,
24 ,,	42 ,,	2·72 ,,
30 ,,	55 ,,	4·25 ,,
35 ,,	70 ,,	4·1 ,,
3 weeks later	78 ,,	4·2 ,,

We see here the usual phenomenon of regeneration, viz. that the number of red corpuscles is restored to normal before the amount of hæmoglobin.

Histologically we find signs of regeneration and of degeneration, as in all forms of severe chronic anæmia. Thus Schaumann (161) describes a diminished rouleaux-formation, poikilocytosis, microcytes, megalocytes, the necrobiotic changes in the protoplasm of the red corpuscles called polychromatophilic, together with nucleated red corpuscles, some of which show mitotic changes in their nuclei. Askanazy also found nucleated red corpuscles, and an unusual number of megaloblasts. There was also "crumbling" of the nuclei of many of the normoblasts (karyorhexis). After two weeks the megaloblasts had disappeared, and there remained only a few normoblasts; in three weeks the latter had also disappeared. The quantity and quality of the leucocytes were normal.

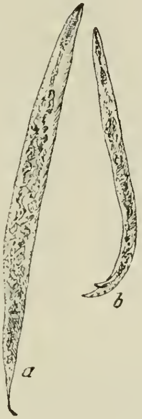
The exact relation of the anæmia to the worm is still obscure. The worm does *not* injure the body by extraction of blood; the degree of oligocythæmia bears no relation to the number of worms in the intestine; *tapeworms may be* *present without any anæmia resulting.* We have therefore to deal with something else besides the mere presence of the worm.

Botkin (154) and Schapiro (155) suggested a reflex change in the blood-forming centres (!) caused by some poison produced by the worm. Wiltschur (163) accepted this view and suggested that the poison was due to a disease of the parasite; whilst Dehio (164) thought that the cause should be attributed to the death of the worm, with subsequent putrefaction and toxic absorption. Schaumann accepts this theory, and draws attention to the absence of free hydrochloric acid in the stomach, which he repeatedly demonstrated; this, he thought, might favour the penetration of the worm into the body. These hypotheses, however, are not supported by the appearance of the worm in the fæces. Even in the cases showing grave anæmia the worm had a normal appearance, and it was often much altered when no anæmia was present. Askanazy has recently made a fresh suggestion. He thinks the cause of the temporary absence of anæmia may lie in the length of time the worm has resided in the body. In some of the cases which he quotes a very long interval (twenty years) elapsed between the entry of the worm and the appearance of anæmia. Whether there is anything in this or not remains to be proved, and can be shown only by observations of a large number of cases.

(*c*) *Anguillula intestinalis seu stercoralis* (Nematodes).—The anguillula that sometimes exist in the human intestine lay eggs, from which embryos or larvæ arise. These are evacuated with the fæces and become mature (*Anguillula stercoralis*). The male is ·88, the females 2·25 mm. long (Fig. 37). The eggs are very similar to those of the Anchylostomum. This parasite was found in 1876 by Normand (165) and Bavay (216) in the fæces of patients in Cochin China, who were suffering from one of the endemic forms of enteric catarrh. A few cases were observed at a later date in Europe, and it was shown (167 to 170) that the distinction originally made between *Anguillula stercoralis* and *intestinalis* was not valid, but that the former was the free form of the latter.

Normand maintained that the diarrhœa caused by the worm produced anæmia. Peroncito (171) contested this view, and claimed that the parasite extracted blood from the body like the *Anchylostomum duodenale.* It is certain that this parasite causes the severest forms of anæmia, which, however, may resolve after its expulsion.

FIG. 37.



2. *Anæmias Secondary to Chronic Infections.*

The most important chronic diseases with which anæmia is often associated are syphilis, tuberculosis, and leprosy.

(*a*) *Syphilis.*—It has long been known that this disease exerts an injurious influence on the blood (175), especially in women. Ricord (176) pointed out the similarity of syphilitic anæmia and chlorosis. Many authors (177 to 181) confirm the statement that there is a diminution of red corpuscles and of hæmoglobin in secondary and tertiary syphilis. More recently Graeber (6), Lezius (182), Müller (183), Rille (184), and Reinert (7) have investigated the condition of the blood in acquired syphilis and the effect of mercury on it. These researches show that though the blood is not much altered, as a rule, the gravest forms of anæmia may result. Red corpuscles and hæmoglobin do not always diminish in equal proportions. Müller, *e.g.*, described four cases of severe anæmia, in one of which the number of red corpuscles was more diminished than the hæmoglobin (720,000 red corpuscles, 18 per cent. hæmoglobin), and Laache describes a similar case. These cases were regarded, in accordance with the theory accepted in those days, as pernicious anæmia following upon syphilis. Lezius investigated the relation between the hæmoglobin and the red corpuscles in the early stages. He found that when the blood was affected at the time of the roseola, the first change was a diminution in the amount of hæmoglobin. In twenty cases he found the same thing, *i. e.* normal or almost normal number of red corpuscles with diminished hæmoglobin, *e. g.*—

6·1175	million	red corpuscles,	77·3	per cent.	hæmoglobin.
4·97	„	„	68·9	„	„
4·76	„	„	68·9	„	„

This is the so-called chlorotic form of blood.

In severe anæmia we get all the signs we might expect—megalocytes, microcytes, poikilocytes, nucleated red corpuscles, and gigantoblasts.

The number of leucocytes is generally normal, even in severe cases. Lezins states that the proportion between the mononuclear and polynuclear cells was normal in his cases. Rille (without actual enumeration) considers that the leucocytes are obviously increased in number, and that the lymphocytes, the eosinophile cells (especially in papular rashes), and the large mononuclear corpuscles all take part in this increase. He also professes to have found isolated marrow-cells in syphilitic blood. Personally I have frequently found a diminution of hæmoglobin in early cases; but I have found the number of red corpuscles, the hæmoglobin, and the number of leucocytes practically normal in some of the severest forms of old visceral syphilis.

We see, then, that one and the same cause, viz. syphilis, may produce alterations of the most different kinds in the blood. This is an excellent illustration of the fact that no appearances in the blood are characteristic of any particular clinical form of anæmia. Thus we have sometimes the appearance (under the microscope) of pernicious anæmia, sometimes of chlorosis. Early forms almost invariably show the latter. In late forms the blood is most often normal, but severe anæmia, when it occurs in syphilis, does so, apparently, only in the later forms. The cause of this occasional appearance of grave anæmia is unknown.

(*b*) *Tuberculosis.*—In describing anæmia due to tuberculosis the locality of the disease is of secondary importance. The tubercular virus may, under certain conditions that are not yet known, give rise to anæmia of moderate degree, and sometimes even grave anæmia, but this is rare. Anæmic blood-changes are most common in chronic tuberculosis (185 to 188). Lacker (187) found in twenty cases that the average percentage of hæmoglobin lay between 38 and 75. Fenoglio (189) obtained similar results. The first accurate estimations were those of Laache (190), who counted the red corpuscles and estimated the hæmoglobin in fourteen cases of pulmonary consumption (cavernous stage). He found the following values:—5·22, 4·9044, 3·76, and 2·408 million red corpuscles. Dehio (191) obtained similar results, viz. that the red corpuscles were sometimes diminished and sometimes normal. He therefore divided the cases into two classes, marasmic and anæmic. In the latter he often observed that the hæmoglobin was more diminished than the number of red corpuscles, *i. e.* the chlorotic condition. We have also the later observations of Neubert (192), Häberlin (193), Grawitz (194), and Strauer (195), which show that chronic tuberculosis does not produce uniform effects on the blood, but that these may be divided into groups.

In the *first group* are the *primary cases*, usually apical, with no fever, and few signs. Here the number of red corpuscles is diminished, that of leucocytes variable. The dry residue of the blood and serum and specific weight are diminished. A greater diminution of hæmoglobin than of red corpuscles is common in this condition (pseudo-chlorosis tuberculosa), *e. g.*—

4·09 red corpuscles	64 per cent. hæmoglobin.
5·32 ,,	82 ,, ,,
5·79 ,,	92 ,, ,,
4·967 ,,	85 ,, ,,

Strauer gives four cases; in three the red corpuscles were diminished (one as low as 2·7 millions), in the fourth normal (5 1 millions). The number of leucocytes in the first stage of pulmonary consumption, if no complications are present, is normal. This is important, for purely tubercular infections of other character (meningitis, peritonitis, etc.) never produce leucocytosis (see above).

In the *second group* we place *chronic phthisis* with formation of cavities, without fever of any degree, and without complications. In these the number of red corpuscles is, according to Strauer, apparently normal, whilst the number of leucocytes lies between 5000 and 10,000. Strauer gives, in this group, values of 4·6 million red corpuscles and 15,000 leucocytes, and of 4·75 million red corpuscles and 12,000 leucocytes. I have also found a normal number of red corpuscles with a *slight degree of leucocytosis* in these cases.

In the *third group* we have the cases accompanied by fever *of hectic character.* Here we have oligocythæmia in conjunction with a proportional diminution of hæmoglobin. The number of leucocytes is very variable, but in this group, no doubt, we have cases of different pathological natures, some with a mixture of infections, and others in which the fever is due to the tuberculous virus (Strumpell [196]). In the severest forms with high fever, in which septic infection is certain, leucocytosis almost always obtains. In other cases, where the fever is due to an acute miliary tuberculosis, there is no leucocytosis. This is important, as it forms, combined with the physical signs and symptoms, an important point in the *differential diagnosis* between acute dissemination and septic infection, on the one side, and the infiltrated form of tuberculosis, the so-called "caseous pneumonia," on the other. In the chronic sepsis of consumption the number of leucocytes is generally slightly increased ; in the infiltrated form there is often a high degree of leucocytosis, almost as much as in croupous pneumonia, and in miliary tuberculosis there is no leucocytosis. Taking these facts into consideration with the absence of leucocytosis in tubercular meningitis, we may conclude that leucocytosis, in cases of tuberculosis with pyrexia, is due to the presence of pyogenic bacilli. Little is known about the other alterations in the blood of tubercular individuals. Freund (197) found a body which he recognised as *cellulose;* Nischimura (198) has recently confirmed this.

Turning to the explanation of the variations in the number of red corpuscles in tuberculosis, I would mention that *sweating* has been held to explain the fact that the initial slight oligocythæmia is replaced by normal amounts of red corpuscles and hæmoglobin; but it is doubtful whether it is the sole cause. Grawitz has shown that the restoration to normal occurs also in those patients who do not sweat; he thinks the change is rather due to the concentration of the blood, which is brought about by the action of tuberculous extract, as this happens experimentally on injection of tuberculous material. Again, the process of breaking down would afford a favourable opportunity for absorption to take place. This explanation is a possible one, but is not yet proved. Another influence may, in my opinion, be at work. During the course of chronic tuberculosis we often find, after a long interval, that the "water-economy" of the patient has altered. The skin, formerly elastic and turgescent, has become lax and wrinkled, and has lost its elasticity and power of absorption. This is especially true of those cases which, according to French authors, are complicated by the uric acid diathesis, and in which Neusser (199) maintains that his perinuclear basophile granules are present. These chronic conditions are associated with a gradual drying up of the body, and must be added to the group that Dehio calls marasmic. In such cases the idea cannot fail to strike us that the normal or almost normal number of red corpuscles is at least partly due to the drying up of the tissues, especially if we remember that in these patients the skin is dry and inactive.

(*c*) *Leprosy.*—Observations of the condition of the blood in this disease are, unfortunately, very few in number. Winiarski (200) examined seventeen cases, and found the same results in the different forms (anæsthetic, nodosa, and mixed). In early cases the blood is normal, and sometimes the number of red corpuscles and amount of hæmoglobin may even be increased. In cases that have lasted a few years the condition of the blood may resemble that found in syphilitic or tubercular pseudo-chlorosis, *i. e.* the number of red corpuscles normal, and the amount of hæmoglobin diminished. Winiarski found, *e. g.*, 5·916 million red corpuscles with 89·8 per cent. hæmoglobin, and 5·741 million red corpuscles with 86·7 per cent. hæmoglobin. In cases in which nutrition has suffered he finds a constant small diminution of red corpuscles with a corresponding loss of hæmoglobin, *e. g.* 4·247 million red corpuscles with 86·3 per cent. hæmoglobin, and 4·688 million red corpuscles with 85·9 per cent. hæmoglobin. In rarer cases higher degrees of oligocythæmia were found, in one case 2·29 million red corpuscles with 54·9 per cent. hæmoglobin. The number of leucocytes was never increased, but varied between 4000 and 8000. According to these observations, then, if there is any change at all in the blood in the early stages of the disease, it is of the so-called "chlorotic" character. Severe cases may show more considerable damage to the blood, and then the loss of hæmoglobin is proportional to that of the red corpuscles. There is an absence of leucocytosis. The disease, from a hæmatological point of view, must be classed with tubercle and syphilis.

(*d*) *In Actinomycosis.*—Bierfreund (188) has described a considerable loss of hæmoglobin, 30—50 per cent. I know of no other estimations.

3. *Anæmia Secondary to Malignant Disease.*

The effect of malignant disease depends not only on the histological nature, but also on the locality of the disease. Dissemination and secondary growths, both of carcinomata and sarcomata, seem to have a distinct influence on the blood.

(*a*) *Carcinoma.*—As a rule the blood is not altered until cachexia occurs. Anæmia of the severest degree is, it is true, met with before this in cases of hæmorrhage, but here it is an indirect result of the cancer: *e. g.* a case of hæmorrhagic cancer of the pylorus in a man 35 years old, in which there was severe anæmia.

Date.	No. of Red Corpuscles.	Hæmoglobin (Fleischl).
22nd July	1,500,000	40
11th August	2,000,000	43
17th August	1,600,000	42
25th August	1,400,000	40
20th September	1,620,000	39
31st October	930,000	22
13th November	1,500,000	25
12th December	950,000	25

These kinds of anæmia are analogous to traumatic cases, and are distinct from those caused by cachexia.

The changes in the blood (192—195, 201—203) due to carcinoma may be summarised by saying that, as in tubercle and syphilis, the amount of hæmoglobin is diminished, whilst the number of red corpuscles remains approximately normal.

Examples :

		Red Corpuscles.	Hæmoglobin.
Osterspey (203)	Carc. Cardiac	5·04	80
	,, Ventr. et hepat.	6·184	87
	,, Œsophagi	8·28	48
Neubert (192)	,, Ventric.	5·085	73
	,, ,,	3·415	34
	,, hepat.	4·918	70
Reinert (7)	,, Ventric.	4·732	51
	,, ,,	6·2	76—78

Thus we have a cancerous pseudo-chlorosis. This is not, however, invariable, as we often find normal relations, and even an increased number of red corpuscles, especially in those cases in which there is a want of fluid in the tissues. The increase in the number of red corpuscles may be accompanied by a corresponding increase of hæmoglobin or by relative oligochromæmia.

In advanced cachexia, even without loss of blood, there is generally oligocythæmia. This, however, is seldom excessive. Strauer (194) gives values of 3·0, 3·325, 3·5, and 4·125 million red corpuscles. The amount of hæmoglobin is often disproportionately diminished even in these cases; *e. g.* Osterspey gives instances of 3·7 million red corpuscles with 40 per cent. hæmoglobin, and 3·96 million red corpuscles with 54 per cent. hæmoglobin. The leucocytosis which exists has been discussed above. It is a common appearance in internal cancer, and is in part due to hæmorrhage, in part caused by the neoplasm itself. Cancers of the uterus and œsophagus generally show no leucocytosis; on the contrary, if there is malnutrition, there may be a diminution of leucocytes. In the latter case the small lymphocytes predominate, a condition characteristic of starvation (Ehrlich). Ebstein (204), using dry preparations, has recently described the appearance of numerous nucleated red corpuscles, both normo- and megaloblasts; he says that the increase of leucocytes consists chiefly of mononuclear cells, and that a few marrow-cells are present. The nucleated cells sometimes showed signs of degeneration ("rosettes and shamrock figures"). We may also mention the increased amount of sugar in the blood of cancer found by Freund (205), and confirmed by Trimpler (206) (see above).

We must now consider how the oligocythæmia, that so often exists, is caused. Some part of it is due to repeated hæmorrhage. Where hæmorrhage is absent, the general opinion now is that the absorption of certain poisons from the neoplasm injures the blood directly and apart from any other action on the metabolism. Whether this is so or not is not yet decided. Recently Grawitz has published an experiment showing that the injection of extract of cancerous masses has exactly the converse effect of that of tuberculous extract. He uses this to support his statement that the anæmia of cancer is due to dilution of the blood.

Rabbit, wt. 2·5 kg.

Time.	Sp. weight of the blood.	Dry residue of the blood.	Dry residue of the serum.
1	1056·4	19·57 per cent.	8·29 per cent.
1·22	Intra-venous injection of 1 c.c. of extract of cancer.		
1·25	1055·5	18·6 per cent.	6·83 per cent.
1·40	1055·5	19·03 „	8·45 „
1·50	Another injection of 1 c.c.		
1·58	1054	18·52 per cent.	7·21 per cent.
2·05	1054	—	—

We see that the results are not so decisive as those found in the experiments with tubercle. We are not, therefore, justified in holding that these relations are constantly present in cancer.

(*b*) *Sarcoma.*—The observations on the blood in this disease are few in number. Hayem gives a case of fibro-osteosarcoma in which the number of red corpuscles was 663,400, *i. e.* severe oligocythæmia. I had two cases of osteosarcoma, one with 1,118,000 red corpuscles, 28 per cent. hæmoglobin, and 68,200 leucocytes, the other with 2,240,000 red corpuscles, 48 per cent. hæmoglobin, and 54,000 leucocytes. Laker (207) describes a case of abdominal sarcoma with 28 million red corpuscles, and 25 per cent. hæmoglobin. He found in a number of cases of sarcoma of bone, values of hæmoglobin varying from 57—100 per cent., whilst Bierfreund (208) found in twenty-nine cases values varying from 40 to 75 per cent.

It appears, then, that oligocythæmia is relatively common in sarcoma. Sufficient observations have not yet been made for us to be able to state the relative proportions of red corpuscles and hæmoglobin. The relations of the leucocytes have been discussed above. The appearance of peptone in the blood has been described by Freund (209) (see above).

The results of operation on malignant tumours.—We might expect that the blood would become normal when the disease was removed. Bierfreund, however, found in seventy-two cases that the amount of hæmoglobin never became greater than it was before the operation. Immediately after operation it was less than before, but this was due to hæmorrhage. This result was obtained even in patients that appreciably increased in weight after the operation. Further, the amount of hæmoglobin remained at its previous level even after an interval of months. This observation, if it be confirmed, is worthy of further study. But we are not at present justified in assuming that the oligochromæmia in cancer and sarcoma is independent of the presence and growth of the tumour.

C. THE BLOOD IN OTHER DISEASES.

1. *The so-called Anomalies of Constitution.*

(*a*) *The hæmorrhagic diathesis.*—The clinical varieties of this are numerous. There are a number of conditions allied to severe scurvy and peliosis rheumatica (210), but in all cases we appear to have to deal with a poison which affects the finest ramifications of the vessels in such a way that hæmorrhages occur spontaneously or from trivial causes. Two influences must then affect the constitution of the blood in these cases; first the amount and rapidity of the hæmorrhages, and secondly the specific actions of the toxic substances. As far as our present knowledge goes the condition of the blood may be explained altogether as the result of hæmorrhages. Thus we get oligocythæmia of all degrees, signs of degeneration and regeneration (polychromatophilia, normoblasts, etc.) in purpura and similar conditions (211—215). The loss of hæmoglobin is said to be approximately proportional to that of red corpuscles (Spietschka [214]). Sometimes a slight transitory leucocytosis is observed.

Some of the old studies of the chemical constitution of the blood in scurvy and allied conditions are of interest. Garrod (216) stated that the amount of potassium in the blood was increased in scurvy, but Lionville, Landrieux, and others found exactly the opposite. Some maintained that there was a diminution of the iron (Chalvet); this, again, was denied by Opitz, Duchek, and Schneider (217). Others claimed to have demonstrated an increase of sodium chloride. Biernacki (18) has made all these statements comprehensible. The authors had no doubt very different degrees of anæmia before them, and Biernacki has shown that different stages of oligocythæmia can produce different effects on the constitution of the blood, and especially on the dry residue.

I give an example of the composition of the blood in a man aged 40, with typical signs of the hæmorrhagic diathesis:

No. of red corpuscles . .	4,600,000
No. of leucocytes . .	13,700

Hæmoglobin (Gowers)	87	per cent.
Density	1055	
In defibrinated blood:		
Specific weight of the blood	1059	
,, ,, ,, serum	1025	
Isotonic co-efficient of red corpuscles	·56	NaCl.
N_2 in blood	2·72	per cent.
,, serum	·924	,,
NaCl in blood	·702	,,
,, serum	·796	,,
Dry residue of blood	20·69	,,
,, ,, serum	8·51	,,
Water of blood	79·31	,,
,, serum	91·79	,,

Volume of serum after Bleibtreu's method was 69 per cent.

(*b*) *Osteomalacia.*—The observation of v. Jaksch (218) that the alkalinity in this disease was diminished was accepted for a time, and the idea (219—222) that the disease was due to a deficiency of lime in the bones, brought about by the action of free acid, was entertained. Fehling (223), however, found that the alkalinity was not diminished in these cases, but was normal, or might even be increased; and recently Levy (224), Beck (226), and myself (225) have in various ways shown the unsoundness of this view. The alkalinity of the blood in osteomalacia varies within normal limits, and the loss of lime in the bones is not to be put down to the simple action of an acid. I found in serum obtained by centrifugalisation ·240 and ·260 per cent. NaOH, *i. e.* normal values.

The number of corpuscles, the amount of hæmoglobin, and the number of leucocytes are usually normal. Neusser states that he has found an increase of the eosinophile cells.

(*c*) *Obesity.*—Leichtenstern (227) and Kisch (228) have published observations of the amount of hæmoglobin in these cases. Kisch found the hæmoglobin increased in 79 (up to 120 per cent., Fleischl) and diminished in 21 out of 100 cases. Leichtenstern found diminution of hæmoglobin in his four cases. Kisch thinks his observations support

Traube's in his division of cases of obesity into two classes, viz. plethoric (*i. e.* polycythæmia) and anæmic. He has noticed that the former is more common in men, the latter in women.

(*d*) *Myxœdema.*—Lebreton (229) examined the blood before and after treatment with thyroid extract. Before treatment the blood showed 1·75 million red corpuscles, 4500 leucocytes, and 65 per cent. hæmoglobin; after treatment for forty days 2·45 million red corpuscles, 9600 leucocytes, and 68 per cent. hæmoglobin. There were nucleated red corpuscles present in the blood, but these disappeared after treatment. The mononuclear leucocytes were said to be increased in number. Lebreton was unable to demonstrate mucin in the blood.

(*e*) *Diabetes mellitus.*—No constant changes are known with exception of the increased amount of sugar in the blood. Some find a certain degree of anæmia, others (230) normal or even excessive numbers of red corpuscles. Reinert gives two cases in which the number of red corpuscles was increased. In my cases the number of red corpuscles was normal. The same is true of the leucocytes, which are present in their usual proportions. I have noticed that the digestive leucocytosis is excessive in severe diabetic cases, even in the absence of previous fasting.

(*f*) *Addison's disease.*—At one time an important part in the production of the pigment was ascribed to the anæmia that occurs in this disease (Averbeck [231]). Later, Nothnagel (232), who showed that it was often absent, thought its appearance was secondary. Severe anæmias have been observed (Pepper, Immermann, Younge [233]). Tschirkoff (234) has recently published comprehensive investigations of the blood in this disease. He found diminished numbers of red corpuscles, *e. g.* of 3·27 millions. He remarks that "few white cells are present." In dry preparations nothing abnormal was seen. Tschirkoff notices one other point, which, if it is confirmed, is important; thus he claims to have found methæmoglobin, apart from his observation that the amount of reduced hæmoglobin is increased.

(*g*) *Gout.*—It is extraordinary that in the enormous literature of this anomalous condition of metabolism there is so little about the constitution of the blood. Garrod (236) succeeded in demonstrating uric and oxalic acids in the blood (see also the results of Klemperer and Weintraud above). Pfeiffer (236) and Drouin (14) found an increase in the alkalinity during the attacks.

Neusser's (199) perinuclear basophile granules have been disposed of above.

Two cases of chronic gout that I examined showed normal numbers of red corpuscles and leucocytes, and a normal amount of hæmoglobin.

2. *The Acute Infectious Diseases.*

The relations of the red corpuscles and leucocytes have already been discussed. I give here some tables showing the chemical constitution in three cases. We see that the volume of serum is often relatively diminished. The blood is poor in chlorine, more especially in pneumonia. The isotonic concentration of the red corpuscles is increased in all cases.

Three Cases of Croupous Pneumonia.

	Zelinka.	*Wessely.*	*Soustek.*
Sp. weight of the blood	1056	1059	1054
,, ,, serum	1025	1026	1022
No. of the blood-cells .	4·56 millions	5·6 millions	5·32 millions
N_2 of the blood .	2·39 vol.-proc.	3·045 vol.-proc.	2·914 vol.-proc.
,, ,, serum .	0·987 ,,	1·083 ,,	0·903 ,,
NaCl of the blood .	0·39 ,,	0·39 ,,	0·422 ,,
,, ,, serum .	0·546 ,,	0·615 ,,	0·682 ,,
Water of the blood .	83·13 wt.-proc.	82·13 wt.-proc.	83·35 wt.-proc.
,, ,, serum .	93·66 ,,	93·58 ,,	94·34 ,,
Volume of the serum .	60·9 proc.	59·8 proc.	52·5 proc.
,, ,, corpuscles	39·1 ,,	40·2 ,,	47·5 ,,

Three Cases of Erysipelas.

	Rektorik.	*Belsung.*	*Reiter.*
Sp. weight of the blood	1054	1056	1056
,, ,, serum	1026	1030	1027
No. of the blood-cells .	5·672 millions	4·872 millions	5·654 millions
N_2 of the blood . .	2·824 vol.-proc.	2·772 vol.-proc.	2·819 vol.-proc.
,, ,, serum . .	0·957 ,,	1·234 ,,	1·0962 ,,
NaCl of the blood .	0·39 ,,	0·455 ,,	0·455 ,,
,, ,, serum .	0·666 ,,	0·65 ,,	0·715 ,,
Water of the blood .	84·77 wt.-proc.	83·47 wt.-proc.	83·03 wt.-proc.
,, ,, serum .	94·0 ,,	92·6 ,,	93·3 ,,
Volume of the serum .	40·7 proc.	51·4 proc.	60·2 proc.
,, ,, corpuscles	59·3 ,,	48·6 ,,	39·8 ,,

Two Cases of Typhoid Fever.

	Knöbl.	*Kaufmann.*
Weight of the blood . .	1055	1054
,, ,, serum . .	1024	1025
No. of the corpuscles . .	5·44 millions	4·309 millions
N_2 of the blood . . .	2·824 vol.-proc.	2·898 vol.-proc.
,, ,, serum . . .	1·0932 ,,	0·957 ,,
NaCl of the blood . . .	0·401 ,,	0·548 ,,
,, ,, serum . . .	0·802 ,,	0·78 ,,
Water of the blood . .	84·0 weight-proc.	84·04 weight-proc.
,, ,, serum . .	93·5 ,,	93·81 ,,
Volume of the serum . .	44·3 proc.	68·96 proc.
,, ,, corpuscles .	55·7 ,,	31·04 ,,

3. *Diseases of the Nervous System.*

A number of acute nervous diseases affect the constitution of the blood, and *vice versâ*. Even in the earliest times anæmia was suggested as a cause of functional disturbances of the nervous system. Recently Reinert (237) has again pointed to a connection between these processes. Out of forty-eight cases of hysteria, 30 per cent. showed only 80 per cent. of hæmoglobin, 47 per cent. between 70 and 80 per cent., 18 per cent. between 60 and 70 per cent., and four cases between 30 and 60 per cent. (Fleischl). In thirty-six cases of neurasthenia, 58 per cent. showed between 70 and 80 per cent. of hæmoglobin, 5 per cent. between 60 and 70 per cent., and the remaining 36 per cent. showed 80 per cent. and over. From my own experience I can confirm the existence of moderate anæmia in neurasthenia.

The chronic diseases, multiple neuritis, tabes, polio-myelitis, dementia paralytica, etc., show sometimes slight degrees of anæmia. The inconstancy of this, however, shows that the cause of the anæmia is to be sought in concomitant circumstances.

4. *Diseases of the Circulation.*

In the majority of cases of chronic heart disease we get signs of concentration of the blood. Thus an increase in the number of red corpuscles and in the density of the blood is usually found (238—243). Some authors, however, state exactly the converse (Leichtenstern [225], Oppenheimer [244], and Stintzing and Gumprecht [9]). In acute cases, too, we get varying relations of red corpuscles and hæmoglobin. The influences at work are not completely understood at present. With regard to cases of organic heart disease, we find that in aortic disease we often, but not always, have a normal or slightly diminished number of red corpuscles; in affections of the mitral valve we have sometimes polycythæmia, sometimes normal and sometimes subnormal values. Diminution of blood-pressure causes dilution of the blood by means of the increased flow of lymph into the vessels, and Grawitz has shown that the first sign of failure of compensation is a diminution in the number of red corpuscles.

This I can corroborate from my own experience.

Example.—S. B—, æt. 16. Mitral disease. While lying at rest no loss of compensation. The corpuscles were counted under these conditions, and again after sufficient movements had been made to produce palpitation.

1. Before 7·50 million red corpuscles . After 6·33.
2. „ 6·475 „ „ . „ 5·93.

Oligocythæmia may also exist without failure of compensation. There must therefore be other influences at work in producing anæmia, especially as many cases of chronic heart disease show polycythæmia, and we are tempted to consider this latter condition as the one characteristic of the disease. How this is caused we do not know. Grawitz attributes it to the concentration of the blood due to disturbances of the "water economy" of the body. The influence of the "water economy" seems to me secondary, for we get variations of the red corpuscles in both directions whether retention of water or polyuria occurs (see table, p. 311).

We see that when most water was lost there was no increase of red corpuscles, but rather a diminution, and that when water was retained the number of red corpuscles was unaltered. Grawitz's idea, therefore, seems improbable. The polycythæmia of heart disease seems to me to be analogous to that of high altitudes, although this is no explanation. Recently Formanek and Haskovek ('Wien. med. Blätter,' 1896, No. 7) have shown that polycythæmia occurs during convulsions. This is to be taken as a sign of increased blood-pressure, which is analogous to the results of diminished pressure.

5. *Diseases of the Lungs.*

Tubercle and pneumonia have already been discussed. Other diseases, *e. g.* emphysema, asthma, and bronchitis, have some influence on the blood: thus asthma and emphysema cause a concentration of the blood with the usual results on the density, red corpuscles, and hæmoglobin. An increase of eosinophile cells, as previously mentioned, is characteristic of asthma. Acute or chronic bronchitis causes leucocytosis according to the nature and duration of the disease. Both catarrhal bronchitis and chronic purulent bronchitis generally run their course with relatively little leucocytosis.

Example.—B. A—, æt. 48. Mitral stenosis and insufficiency, ascites, and dropsy.

Date.	Medicine.	Quantity of urine.	No. of red corpuscles.	Body weight.	Remarks.
Dec. 28	Digitalis	400 cm.^{3}			
,, 29	Diuretin	1200 ,,			
,, 30	,,	1400 ,,			
,, 31	,,	1000 ,,			
Jan. 1	Calomel	900 ,,			
,, 2	,,	600 ,,			
,, 3	,,	700 ,,			
,, 4	Diuretin	1200 ,,		94·4 kg.	
,, 5	,,	1700 ,,	6,575 mill.		
,, 6	,,	1400 ,,	7,600 ,,		
,, 7	Digitalis+Diuretin	1600 ,,			Diarrhœa
,, 8	,,	1400 ,,			,,
,, 9	,,	2100 ,,			
,, 10	,,	2000 ,,	8,100 ,,		
,, 11	,,	2000 ,,			
,, 12	,,	2000 ,,			
,, 13	,,	1400 ,,	7,655 ,,		
,, 14	Calomel	1400 ,,	6,725 ,,		
,, 15	,,	1200 ,,			
,, 16	,,	1800 ,,			Diarrhœa
,, 17	,,	2200 ,,	6,660 ,,		,,
,, 18	Calomel+Digitalis	2900 ,,			,,
,, 19	Decoct. Juniperi	3600 ,,	5,675 ,,		,,
,, 20	,,	6000 ,,		87 kg.	
,, 21	,,	3600 ,,	6,500 ,,		
,, 22	Calomel	4100 ,,			
,, 23	,,	3600 ,,			
,, 24	,,	2000 ,,	6,140 ,,		
,, 25	Strophanthus	2600 ,,			
,, 26	,,	1500 ,,			
,, 27	,,	1200 ,,	6,900 ,,		
,, 28	,,	1500 ,,			
,, 29	,,	1200 ,,			
,, 30	,,	1200 ,,			
,, 31	,,	1200 ,,	7,280 ,,		
Feb. 1	,,	1200 ,,			
,, 2	,,	1200 ,,	6,300 ,,	69·2 kg.	
,, 3	,,	1300 ,,			
,, 4	,,	1400 ,,			
,, 5	,,	1400 ,,			
,, 6	,,	1400 ,,			
,, 7	,,	1400 ,,	6,370 ,,	73·0 kg.	
,, 8	,,	1400 ,,			
,, 9	,,	1800 ,,			
,, 10	,,	1500 ,,	6,735 ,,		

6. *Diseases of the Kidneys.*

One effect of the blood, viz. the loss of albumen, is common to the different forms of nephritis. In the various forms different influences of course come into play, *e.g.* leucocytosis which is due to the scarlatina and not to the kidneys may persist for a long time in scarlatinal nephritis. In other cases, if hæmorrhage occurs, the blood may be appreciably influenced; therefore acute, subacute, and chronic nephritis demand a separate discussion. As observations, however, have usually been made with regard to nephritis in general, and without specification of the variety, we are at present unable to do more than give a rough account of the general changes. It is usually recognised that the blood in renal disease is richer in water and poorer in albumen than in normal (245) conditions. The amount of the existing oligocythæmia and hypalbuminosis depends, no doubt, on the amount of the hydræmia present. Thus Sörensen, in eight cases of chronic nephritis, found an average number of 4·74 million red corpuscles, and Reinert 4·05 million in a case of chronic parenchymatous nephritis. The specific weight of the blood is usually lowered, not only by the loss of red corpuscles, but also by the diminished density of the serum. Concentration of the blood may occur if diuretics are given (in œdema). The degree of oligocythæmia is generally small, but may become large if hæmorrhage occurs. In such cases the number of red corpuscles may descend to 1·5 or 1 million. The hæmoglobin is approximatively proportional to the number of red corpuscles. In the majority of cases the number of leucocytes is slightly increased (246). The eosinophile cells are also said to be increased in number. None of these changes are at all characteristic, so that the condition of the blood is hardly of any value in the diagnosis of the disease.

Analysis of two cases, one of contracted kidney with fatty degeneration of the heart, and one of chronic parenchymatous nephritis with hæmorrhage, both fatal :

TABLE.

	Posch.	*Kamerer.*
Sp. weight of the blood . .	1051	1040
„ „ serum .	1023	1023
No. of the red blood-cells .	4·42 millions	1·928 millions
N_2 of the blood . . .	2·457 vol.-proc.	1·932 vol.-proc.
„ „ serum . . .	0·794 „	1·01 „
NaCl of the blood . . .	0·9061 „	0·631 „
„ „ serum . . .	0·822 „	0·526 „
Isotonic concentration . .	0·46 proc. NaCl	0·4 proc. NaCl
Water of the blood . .	85·2 weight-proc.	88·98 weight-proc.
„ „ serum . .	94·5 „	93·87 „
Volume of the serum . .	79·8 proc.	77·49 proc.
„ „ corpuscles .	20·2 „	22·51 „

Uræmia is a condition in which the excretion of the constituents of the urine fails. In view of Frerichs' work we are justified in considering it as a condition of poisoning, but we are still unable to describe the particular poisons at work. Frerichs (247) considered urea, Perls (248) kreatinin, as the essential poisons; but these authors were soon contradicted, partly by their own work and partly by Landois (249), who demonstrated that the most widely different constituents of the urine can, when applied to the cerebral cortex, produce symptoms similar to uræmia. Feltz and Ritter (250) and Astaschewsky (251) simultaneously published observations tending to show that uræmia was caused by poisoning with potash salts. They found that potassium increased in the blood of dogs when death was caused by ligature of the ureters. Shortly afterwards Snyers (252) and Horbaczewski (253) denied the correctness of these statements. More recently Bouchard (254), Roger (255), and Rovighi (256) have accepted the potassium theory in a modified form. These authors do not consider that all the complex uræmic symptoms can be attributed to one single substance, but that they are due to intoxication by a number of more or less poisonous bodies, amongst which potassium salts have an important place. Other authors attribute uræmia to influences of quite a different character. v. Jaksch (257) found that the alkalinity of the blood was much diminished in uræmia, and suggested the possibility of an acid poison. I had occasion to examine the blood of a uræmic individual after venesection. Using my method of coagulation, I found very low values for the alkalinity. For the whole blood the alkalinity = 132 per cent. NaOH, and for serum obtained by spontaneous coagulation = 100 per cent. NaOH, so that this observation fully confirmed v. Jaksch. We have not yet, however, a sufficient number of observations to be able definitely to state whether this is due to the uræmia or to accidental concomitant circumstances. Some experiments in dogs fail to give support to the theory that artificial uræmia is produced (see below) by acid poisoning.

We have no positive data to go on if we wish to ascertain the causes of such a diminution of alkalinity. v. Jaksch (258) in a later paper has demonstrated an increase of uric acid in the blood of nephritis which is sometimes not inconsiderable. This is not, in itself, great enough to account for the diminution of alkalinity; besides, in the same publication v. Jaksch has shown that an increase of uric acid may occur in very different conditions, especially in diminished oxidation of the blood. It seems improbable, therefore, that uric acid plays an important part in the production of the diminished alkalinity in uræmia.

We have no proof of an increased quantity in the blood of the other acids which have been mentioned by various authors, viz. fatty acids, lactic acid, phosphoric acid.

We are not in a much better position when we try to explain the experimental uræmia produced in animals by ligature of the ureters or extirpation of the kidneys. Feltz and Ritter found an increase of potassium. Snyers denied this. I (259) found it increased from ·026 per cent. to ·127 per cent. KCl after death, but I was never able to find this increase on examination of the blood during life, not even when I examined it just before death.

	Normal blood. per cent.	Uræmic blood. per cent.
Dog I	·0498 KCl	·0485 KCl.
Dog II	·05717 KCl	·0546 KCl.

I also failed to find signs of any acid poisoning in these experiments. There appeared to be rather an increase than a decrease of carbon dioxide.

Normal dog. per cent.	Uræmic dog. per cent.
36·08 vol. CO_2 . . .	35·6 vol. CO_2.
42·09 " . . .	50·35 "
36·6 " . . .	45·36 "

I further found no appreciable increase of phosphoric acid.

Normal.	Uræmic.
·0603 Na_2HPO_4 . .	·0742 Na_2HPO_4.
·0539 " . .	·0592 "

It seems, then, that in dogs the cause of uræmic poisoning is not to be found in potassium acid or phosphorus alone, but it is possible that the potassium salts play some part in the production of the symptoms. In spite of the fact that neither Snyers nor myself was able to find an increase, it is possible, when we take into consideration the fact that the toxic dose of potassium salts is very low (*e. g.* 18 per kilo. according to Bouchard), that this may exist, although it is not large enough to be recognised by our present methods. Some of the cardiac features of uræmic dogs resemble those of potassium poisoning, so that this possibility must be kept in view. In any case potassium poisoning cannot be considered as the only cause of the symptoms. Other constituents or derivatives of the urine must be at work. The toxic action of urine is of a complex nature according to Bouchard, Tarnier, Chamberlent, and Laulanier, who have been working in this direction. Bouchard distinguishes seven toxic substances in the urine: a diuretic (urea), a narcotic, a salivator, a myotic, an antipyretic, and two substances, one organic and one—the potassium salts of the urine—inorganic, which produce convulsions. We can partly understand the conditions if we assume that these substances are absorbed simultaneously. Again, the different types of uræmia may be due to differences in the quantities of the toxins which are absorbed.

The condition of the blood in uræmia is in no way characteristic. The number of red corpuscles and leucocytes generally varies between normal limits, unless anæmia has previously obtained. Uræmia itself causes no alteration in the red corpuscles. I have observed an increase of platelets, apparently due to the oligocythæmia present. The most remarkable point, beyond the diminished alkalinity, is the relatively high amount of nitrogen in alcoholic extracts of the blood and serum. This is probably due to the increased amount of urea. Pick (260) and I found as much as 1 per cent. N_2 in the serum. The isotonic concentration of the red corpuscles in dogs shows no appreciable difference before and after ligature of the ureters :

	I.	II.
Isotonic concentration before . .	·47	·52
,, shortly before death . .	·46	·5

7. *Diseases of the Liver.*

In most of these, except atrophic cirrhosis, the blood is altered by the presence of bile constituents. The clinical condition is usually called *cholæmia.* The poisonous action of bile on the body is apparently exclusively due to the bile acid salts it contains. Another substance, viz. cholesterine, has also been assumed by some to play a part in the poisonous action. This, however, is not proved, for though some (Flint Harley [261]) have found an increase of cholesterine in the blood of jaundice, no indifferent substance in which cholesterine is soluble has been found. The alteration of the blood in cholæmia is more marked macroscopically than under the microscope. The blood is characterised by a yellowish-red play of colours, which sometimes merge into light orange, after coagulation or defibrinisation : the serum is of a brownish-yellow colour, it gives the reaction of the bile pigment, and on heating to 56°—60° C. becomes an intense grass-green (v. Jaksch [262]).

Microscopically the blood does not appear to be altered. The other chief characteristics of icteric blood are its relation to salt solutions, the alteration in volume of the red corpuscles, and certain changes in its chemical constitution. It is especially remarkable that the resistance of the red corpuscles to water and dilute saline solutions is distinctly above the normal, *i. e.* that the isotonic concentration of the red corpuscles is very low. This I have observed in every case of jaundice which I have examined. Normally a solution of sodium chloride requires to have a concentration of ·46 to ·48 per cent. to prevent the red corpuscles from breaking up (263), but in jaundice a concentration of ·4 per cent. or ·38 per cent. is sufficient. The cause of this change is not known. I have suggested that the most fragile of the red corpuscles are dissolved owing to the presence of the bile acid. It would follow that the apparent excessive resistance is due to the fact that only the strongest are left. This assumes that the hypertonic value of the serum sinks below the normal isotonic limits when bile acids are present, and also that in jaundice the number of red corpuscles is diminished. Neither of these assumptions is true. I found the hypertonic value of the serum twice as great as is necessary to preserve the red corpuscles (·76 and ·864 per cent. NaCl). In jaundice due to obstruction the number of red corpuscles is normal or may be slightly increased. There is therefore no destruction of red corpuscles, and my theory falls to the ground. As we said above, it seems probable that the isotonic concentration of the red corpuscles is not influenced merely by osmosis. Hoppe-Seyler suggested that there is an intimate connection between the hæmoglobin and the stroma of the red corpuscles, and it is possible that this relation might be affected in such a way that the dissociative action of water would be resisted. The blood of jaundice is rich in nitrogenous bodies and poor in chlorides; the volume of the cells seems to be larger than normal. I give two examples of analysis of the blood in catarrhal jaundice.

		Leherbauer.	*Sirimek.*
Isotonic		0·36 proc. ClNa	0·38 proc. ClNa
Hypertonic concentration of serum		0·864 ,, ,,	0·76 ,, ,,
Sp. weight of the blood		1052	1054
,, ,, serum		1026	1028
Alkalescence of the blood		0·300 proc. NaOH	0·240 proc. NaOH
,, ,, serum		0·140 ,, ,,	0·146 ,, ,,
NaCl of the blood		0·4387 proc.	0·397 ,,
,, ,, serum		0·5382 ,,	0·573 ,,
N_2 of the blood		3·29 ,,	3·52 ,,
,, ,, serum		1·225 ,,	1·14 ,,
Dry residue of the blood		18·7 ,,	22·29 ,,
,, ,, serum		8·7 ,,	7·73 ,,
Water of the blood		81·3 ,,	77·71 ,,
,, ,, serum		91·3 ,,	92·27 ,,
No. of red cells		4·075 millions	5·234 millions
Bleibtreu	Vol. of the serum	19 proc.	23 proc.
	,, ,, corpuscles	81 ,,	77 ,,
Control experiment	Vol. of the serum	23 ,,	26 ,,
	,, ,, corpuscles	77 ,,	74 ,,

The relative diminution in the volume of the serum, if it is confirmed, must be the chief cause of the poverty of the total blood in salts. The serum, further, is poorer in chlorides than usual, possibly owing to the replacement of the salts by bile acid products. The increase of volume of the red corpuscles is considerable, but its significance is at present obscure.

Diseases of the liver cause alterations in the blood even in the absence of jaundice, owing to the important part played by this organ in the formation of blood. Thus we often get oligocythæmia, which may be of high degree (I had one case with only 1·5 million red corpuscles), in atrophic cirrhosis; but this may improve or disappear when the existing ascitic fluids are withdrawn. It is more than probable that these conditions are due to the transitory effects of concentration, for fluid when withdrawn from the abdomen is quickly replaced, its source being no doubt partly from the blood.

Hayem has described an abnormal viscidity of the red corpuscles in some forms of chronic cirrhosis. There is no uniform change in the leucocytes. Acute inflammations or hepatic abscesses cause, like all inflammatory processes, leucocytosis of the polynuclear type. Thus I found 26,000 leucocytes in a case of acute cholecystitis (due to stone) with high fever. A case of abscess with repeated rigors showed 32,000 leucocytes.

In simple catarrhal jaundice, if uncomplicated, there is no leucocytosis, but carcinoma of the liver is often accompanied by a slight increase in the number of white cells. In cirrhosis the number of leucocytes follows no rule, and it is not known on what circumstances the appearance of leucocytosis in this condition depends.

8. *Diseases of the Digestive Organs.*

Acute diseases of the stomach and intestine, *e. g.* acute toxic gastritis and enteritis, do not as a rule exert much influence upon the blood, and then only by the concentration which follows profuse diarrhœa. In children their influence is very different. Sometimes, however, we get a leucocytosis due to the poison introduced or formed in the body. In adults the most important changes are those caused by gastric ulcer and by chronic catarrh of the stomach, with secondary atrophy of the mucous membrane. Both of these may cause the severest degrees of oligocythæmia, as may atrophy of the gastric glands (Klinkut [264] and Henry and Osler [265]). These authors have attributed the cause of pernicious anæmia to this atrophic condition. In the section on chlorosis I gave a case in which atrophy of the intestinal mucous membrane produced similar effects and showed oligochromæmia.

For a long time changes in the blood were thought to afford an important point in the differential diagnosis between gastric ulcer and carcinoma (Häberlin [266]). The value of this has been correctly estimated by Osterspey (203). The gravest anæmia may occur in gastric cancer, and oligochromæmia is often found in less severe forms. The same changes are also found in gastric ulcer. Leichtenstern (227), Reinert (7), and Osterspey all observed a relative diminution of hæmoglobin in cases of gastric ulcer.

They describe instances of 3·692 million red corpuscles with 12 per cent. hæmoglobin (!), and of 2·64 million red corpuscles with 30 per cent. hæmoglobin.

This chlorotic condition is not always found in gastric ulcer, the diminution of red corpuscles and of hæmoglobin being often proportional. Thus Osterspey gives instances of 1·9 million red corpuscles with 31 per cent. hæmoglobin, 3·296 million red corpuscles with 70 per cent. hæmoglobin, and of 4·048 million red corpuscles with 84 per cent. hæmoglobin.

There is generally a moderate leucocytosis in gastric ulcer after hæmorrhage, but this may disappear in a few days if the hæmorrhage does not recur.

It is hardly necessary to repeat that we may get all the changes which occur in grave anæmia in severe anæmias caused by gastric ulcer, viz. the presence of poikilocytes, microcytes, normoblasts, megaloblasts, etc.

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APPENDIX.

THE ANÆMIAS OF CHILDHOOD.

THERE are some physiological differences from adult blood in the first days of life besides the polycythæmia and leucocytosis mentioned above. With regard to the red corpuscles, Hayem (1) notes the significant differences in size of the individual cells of the new-born, and Hoffmeier (2) maintained that the central depression was absent. Fischl (3), who recently studied these relations, confirmed Hayem's, but denied Hoffmeier's observation. The appearance of nucleated red corpuscles in the blood of healthy new-born infants was considered normal by Kölliker (4) and Neumann (5). This view has been modified by Hayem, Luzet (6), and Fischl, who state that the presence of these nucleated cells is physiological in the last months of fœtal life, and that a few may be found in the blood of mature infants after birth. Mitotic division has never been noticed in the nuclei in health. The condition of the blood in premature infants varies according to the age—normo- and gigantoblasts are found in very premature infants, but are either absent or very few in number if birth takes place near or at the normal time. Duperie and Luzet have stated that in the first weeks of life the mononuclear elements of the leucocytes preponderate. Fischl, however, found approximately the same proportion of the different leucocytes as in adults. Hock and Schlesinger (7) and Zappert (8) describe a relative abundance of eosinophile cells in the blood of children. Changes in the blood, especially anæmia, are relatively common in sick children. It is customary to divide the different clinical forms of this anæmia into acute and chronic, and into primary and secondary forms.

Primary acute anæmia, such as is caused by severe hæmorrhage, shows the same changes in the blood as in adults.

All the forms of *primary chronic anæmia* which occur in middle-aged people are described in early childhood. They are not, however, so commonly found. We have observations of *pernicious anæmia* in children by many authors (9—13). It seems to me, however, that these cases ought really to be classed as severe secondary anæmias.

Leukæmia in children has been often observed, and (14—19) cases have been described at as early an age as twelve or fourteen months. There do not seem to be any important differences between the changes of the blood or organs in the same diseases in children and adults. Those conditions called pseudo-leukæmia are more numerous in children than in adults, as certain additional causes are brought into play, such as scrofula, rickets, congenital syphilis, and chronic diseases of the digestive organs. We shall consider these changes separately; in the meantime we must discuss a clinical form of anæmia which is supposed to be characteristic of childhood, viz. the so-called—

ANÆMIA PSEUDO-LEUKÆMICA INFANTUM.

In 1889 v. Jaksch (10) described a new pathological condition in children as follows:—"We find considerable swelling of the spleen, liver, and lymphatic glands, and very considerable and persistent leucocytosis (1 to 20, 1 to 17, or 1 to 12). Nevertheless the condition anatomically is not leukæmia." He gave the above name to this disease, and described three cases (20). The number of red corpuscles was much diminished (820,000 and 1,380,000), that of leucocytes much increased (54,600, 114,150, etc.). In dry preparations v. Jaksch found an absence of platelets, the Maragliano signs of degeneration of red corpuscles, poikilocytes, very few eosinophile cells, and a preponderating number of polynuclear leucocytes. He found in one case "white corpuscles containing red corpuscles." In view of the rarity of this last feature further details would be interesting. Hayem has described a case similar to these, in which he found, in addition, nucleated red corpuscles. His pupil Luzet (6) found mitotic divisions in these, and Hock and Schlesinger (7) thought this last feature was characteristic of anæmia pseudo-leukæmica infantum. Further observations have been made by Baginsky (21), Senator

(22), Fischl (23), Andeoud (24), Monti and Berggrün (17), Felsenthal (25), and others, whilst some Italian authors (Fede [26]) described similar conditions under the name of "anæmia splenica infettiva dei bambini" even before v. Jaksch published his description. Jaksch and most authors, in consideration of the conditions of the blood and organs, associated with this disorder, considered it a special disease, and contrasted it with true leukæmia. This view has been contested by Fischl, Raudnitz, and Epstein (27). Fischl pointed to the fact that there was no uniform relation between the changes of the blood and those of the organs, and that "in a great number of the cases influences were at work that we know can cause the severest anæmic cachectic conditions." This is true, and the idea cannot fail to strike us that the authors have mixed up a number of different conditions under the name of anæmia pseudo-of leukæmica infantum, just because they found a diminution red cells and considerable leucocytosis, but no true leukæmia. We know that many pathological conditions may cause such changes. We find a number of cases of rickets and congenital syphilis in Monti and Berggrün's tables, "anæmia gravis cum leucocytosi;" and this is also true of the published cases of anæmia pseudo-leukæmica infantum. Fischl found in eighteen recorded cases sixteen of severe rickets, and two of congenital syphilis. The fact that nucleated red corpuscles with signs of mitosis may appear in the adult in severe anæmia throws considerable light upon the observations of Hayem, Hock and Schlesinger, etc. I do not consider that anæmia pseudo-leukæmica infantum is a distinct and special form of disease.

Owing to the peculiarities of metabolism in childhood anæmia is more easily produced, and is not infrequently due to relatively trivial causes. The origin of these secondary anæmias in children, as in adults, is often obscure. It is sometimes difficult to decide whether the condition is one of deficient production or increased destruction of red corpuscles. In later periods of the disease both of these, as in adults, must frequently be at work.

Certain anomalies of constitution, such as tubercle, congenital syphilis, and rickets, play the most important part in the ætiology of anæmia in childhood. Catarrhal affections of the digestive passages must be included, whilst conditions such as malignant tumours are of much less importance in childhood than in adults. The alteration in the blood generally corresponds to the degree of the existing local or general disease. Thus we may get various degrees of oligocythæmia in which the amount of hæmoglobin undergoes the same relative variations as in the adult. Signs of regeneration may also appear, but in what cases and in what degree are not clear. The alteration in the number of leucocytes is dependent only to a slight extent on the intensity of the anæmia. Many other concomitant circumstances, viz. differences in concentration of the blood, influence of chemiotactic substances, poisons, etc., are of more importance.

(1) *Anæmia in hereditary syphilis.*—Laache (27) was the first to describe a diminution of red corpuscles in congenital syphilis. Later, Luzet (6) published similar observations, and since then many cases of grave anæmia due to congenital syphilis have been described, so that we may consider anæmia as a not uncommom complication. The amount of diminution of the red corpuscles varies between wide limits; sometimes the hæmoglobin is diminished in proportion, sometimes we get the chlorotic form of anæmia (28, 29). There is generally a small amount of leucocytosis. Values of 12,000 or 14,000 are common, but Loos says that in cases of severe anæmia the number may be much greater. Baginsky (21) even speaks of true syphilitic leukæmia. Loos found as many as 58,000 leucocytes. It is not certain that these high degrees of leucocytosis are due wholly to the syphilis.

Loos further found numerous micro- and megalocytes, together with nucleated red corpuscles (chiefly normoblasts). The changes towards aniline dyes, called polychromatophilic by Gabritschewsky (30), (probably a sign of degeneration), were found in the non-nucleated red corpuscles. The quantity of the leucocytes varies greatly. Loos found 15·9 to 33·7 per cent. lymphocytes, 26·4 to 58·7 per cent. polynucleated leucocytes, but very few transitional forms (22 to 52·9 per cent.). Fischl found the same. Loos states that the more pronounced the rash, the greater the number of eosinophile cells. He refers to the analogy of the increase of the eosinophile cells in other dermatoses (Neusser [31], Zappert [6]). He also found marrow cells and leucocytes with basophile granules. There is little that is specific in these changes, the most remarkable being the constant leucocytosis (although usually of moderate degree) and the presence of marrow cells and basophile leucocytes.

Possibly insufficient or delayed formation of blood is at the bottom of the blood changes in this condition, but we have no certain proof of this. It is only the absence of signs of destruction of red corpuscles, and the fact that the children are often immature, that cause me to think that the amount of blood formed is not so large as in mature healthy children.

(2) *Anæmia in rickets.*—Anæmia is rarely absent in severe rickets. v. Jaksch describes a case in which the red corpuscles sank from 1,600,000 to 750,000 within three months, and Luzet one in which they sank from 2·11 to 1·596 millions in three weeks. Hock and Schlesinger give the average number of red corpuscles in rickets, with and without splenic enlargement, as 2·5 millions. The hæmoglobin is usually proportionately diminished. The leucocytes are said to be always increased in number. The red corpuscles show polychromatophilic signs, and often normoblasts are present. The increase of leucocytes consists chiefly of polynuclear neutrophile cells. An increase of eosinophile cells does not seem to be the rule. Loos states that he has found mast cells and mitosis in the nuclei of the leucocytes. Of these statements the presence of leucocytosis is the most remarkable, and must be due at any rate in part to the rickets itself. This is seen in a case of Hock and Schlesinger, a child sixteen months old with rickets but with no anæmia, in which the number of leucocytes was 45,000. No doubt the intestinal catarrh which generally obtains is also an effective cause of the leucocytosis in the majority of cases.

(3) *Anæmia in gastro-intestinal inflammations.*—In childhood the changes in the blood are of practical importance owing to the frequency of these conditions. Disturbances

of digestion cause oligocythæmia in children as in adults. This is not due to starvation, but to the action of hæmolytic substances probably formed in the intestine. In *acute gastritis* of children the important change is not a diminution of red corpuscles, but an increase in the number of white cells. Fischl gives such a case, and speaks not of anæmia, but only of leucocytosis. Hock and Schlesinger give a similar case, lasting three days, where there were also signs of anæmia—3·9 million red corpuscles and 38,000 leucocytes, together with a few nucleated red corpuscles. The authors all agree in finding a condition of lymphocytosis, *i. e.* the increase of leucocytes was composed of small white cells originating from the lymphatic glands. Fischl found that the lymphocytes formed 59·48 per cent. of the total leucocytes. *Chronic catarrh* of the gastro-intestinal canal is often accompanied by a greater degree of anæmia. Thus Hayem (32) gives a case in a child two months old, with 685,000 red corpuscles and 18,910 leucocytes. A large number of cases are recorded, but they are generally combined with rickets, congenital syphilis, or tubercle. The only conclusion we can come to at present is that the most variable degrees of anæmia may be caused by these intestinal lesions. The remarkable point is the increase of lymphocytes. In severe cases of anæmia we of course get all the usual signs —microcytes, poikilocytes, etc.

(4) *Anæmia in tuberculosis.*—Tubercle of the glands in children is of most practical importance. The relation of the blood in the adult has been carefully investigated (Grawitz [33], Strauer [34]), but not so in children. Published data are few in number, and only state the frequency of variably high degrees of anæmia in chronic tuberculosis of the lungs or of the glands. The leucocytes are stated to be usually increased. Thus Monti and Berggrün give a case of glandular tubercle in a boy aged six and three quarter years, with 3·64 million red corpuscles, 14,000 leucocytes, 38 per cent. hæmoglobin, and specific weight of blood 1040; and one of chronic tuberculous peritonitis and phthisis in a girl aged seven years, with 3·23 million red corpuscles, 17,200 leucocytes, 52 per cent. hæmoglobin, and specific weight 1043. The relatively large

diminution of hæmoglobin compared with that of red corpuscles is remarkable. In both cases the increase of leucocytes was composed chiefly of the polynuclear cells. The eosinophile cells are often found to be increased in the blood of children suffering from tuberculous diseases, as is the case in adults.

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